

CANCER OF THE TONGUE IN FINLAND

Incidence, detection, survival and prognostic factors

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FINLAND**

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Abstract

A population-based study was conducted to determine the trends in incidence and survival of cancer of the mobile tongue in Finland over the past 40 years. Possible changes in patient and tumour characteristics, early detection and prognostic factors of cancer of the mobile tongue were monitored in a geographically defined area of Northern Finland over the past 20 years. There were 1504 new cases with cancer of the mobile tongue in 1953-1994 in Finland and 105 cases in 1974-1994 in Northern Finland. An increasing trend in incidence of cancer of the mobile tongue was observed over the past 20 years both nationwide and in Northern Finland. The stage distribution of the cancer of the mobile tongue remained very much the same throughout the study period. Despite the increasing incidence rate and unchanged stage distribution of the tumours, the 5-year relative survival rate of cancer of the tongue improved from 40% to 58% in the 40-year study period in Finland.

To evaluate the detection of cancer of the tongue, patients' primary care files were reviewed. It was revealed that the diagnostic skills of the physician/dentist first contacted by the patient had a significant effect on the patient's prognosis. If the cancer was not detected at the primary visit and no follow-up was scheduled, the delay was often fatally long. The most important factor influencing the referral pattern was the patient's primary symptom at the initial visit. The more closely the symptom was related to the tongue, the more likely the patient was correctly referred.

To recognise aggressively behaving early stage (Stages I-II) cancers of the tongue, various prognostic factors were analysed. It was observed that an old age (65+years) of the patient, a high malignancy score of the tumour and the absence of p53 predicted poor prognosis in early stage carcinomas. Patients with these qualities may require more aggressive initial therapy.

Keywords: epidemiology, prognosis, oral cancer.

To Siiri

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Oulu, November 2000

Saara Kantola

Terminology

Criteria for cancer of the tongue – in the present study, squamous cell carcinoma of the mobile tongue was defined as cancer of the tongue. The mobile tongue consists of the anterior 2/3 of the tongue.

Prevalence - proportion of the population that has the disease at certain point of time.

Incidence rate – number of disease onsets in the population divided by the sum of the person-years of follow-up for all individuals in the population.

Relative survival rate – ratio of the observed survival of a given group of patients to the expected survival in a corresponding group of the general population.

Disease-specific survival rate - proportion of patients alive after a certain period of time from the diagnosis of the disease. Deaths due to other causes than the disease studied are censored.

Mean disease-specific survival time – mean of the times the patients survive after the diagnosis of the disease. Deaths caused by other causes are regarded as censored data.

75th percentile disease-specific survival time - time which 75% of the patients survive after the diagnosis of the disease. Deaths caused by other causes are regarded as censored data.

TNM classification of oral tumours

T	Primary tumour
Tis	Pre-invasive carcinoma (carcinoma <i>in situ</i>)
T0	No evidence of primary tumour
T1	Tumour 2cm or less in its greatest dimension
T2	Tumour more than 2cm, but not more than 4cm in its greatest dimension
T3	Tumour more than 4 cm in its greatest dimension
T4	Tumour with extension to bone, muscle, skin, antrum, neck etc.
TX	The minimum requirements to assess the primary tumour cannot be met
N	Regional lymph nodes
N0	No evidence of regional lymph node involvement
N1	Evidence of regional lymph node involvement in movable homolateral lymph node, the node 3 cm or less in its greatest dimension
N2a	Evidence of regional lymph node involvement in one homolateral node, the node more than 3 cm, but less than 6 cm in its greatest dimension
N2b	Evidence of regional lymph node involvement in several homolateral regional lymph nodes, the nodes less than 6 cm in their greatest dimension
N2c	Evidence of regional lymph node involvement in bilateral or contralateral regional lymph nodes, the nodes less than 6 cm in their greatest dimension
N3	Evidence of involvement of fixed regional lymph node, the node more than 6 cm in its greatest dimension
NX	The minimum requirements to assess the regional lymph nodes cannot be met
M	Distant metastases
M0	No evidence of distant metastases
M1	Evidence of distant metastases
MX	The minimum requirements to assess the presence of distant metastases cannot be met

Stage grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-3	N1	M0
Stage IV	T4	N0, 1	M0
	Any T	N2, 3	M0
	Any T	Any N	M1

List of original articles

This study is based on the following articles, which are referred in the text by Roman numerals:

- I Alho O-P, Kantola S, Pirkola U, Läärä E, Jokinen K & Pukkala E (1999) Cancer of the mobile tongue in Finland - Increasing incidence, but improved survival. *Acta Oncol* 38:1021-1024.
- II Kari S, Alho O-P, Jokinen K, Hyrynkangas K & Läärä E (1997) Carcinoma of the oral tongue in Northern Finland: trends in overall incidence and patient and tumour characteristics. *J Oral Pathol Med* 26: 480-483.
- III Kantola S, Alho O-P, Jokinen K & Hyrynkangas K (2000) Detection of tongue cancer in primary care. Submitted to *Br J Gen Pract*.
- IV Kantola S, Parikka M, Jokinen K, Hyrynkangas K, Soini Y, Alho O-P & Salo T (2000) Prognostic factors in tongue cancer - Relative importance of demographic, clinical and histopathological factors. *Br J Cancer* 83: 614-619.

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1 Introduction

The incidence of cancer of the tongue has increased over the past decades both in Europe and in the United States. (Macfarlane *et al.* 1992, Swango 1996). The increase in incidence has been especially obvious among young men under 40 years of age. The increasing consumption of tobacco and alcohol in the western industrialised countries has been blamed for this trend (Møller 1989, Macfarlane *et al.* 1992). However, tobacco and alcohol have not proven to be equally significant risk factors for cancer of the tongue as for cancer of the floor of the mouth (Franceschi *et al.* 1992, Barasch *et al.* 1994). Thus, the reason for the increase in incidence remains partly unknown.

Cancers of the tongue are, even today, quite sizable at the time of diagnosis. The asymptomatic nature of the disease has been considered one reason for this (for a review, see Prince & Bailey 1999). It has also been noted that public campaigns and the growing public knowledge have not had any influence on patients' activity to seek medical advice after the onset of cancer symptoms (Wildt *et al.* 1995). This is unfortunate as the clinical stage of the tumour at the time diagnosis is the most important prognostic factor of the cancers of the oral cavity (Ghouri *et al.* 1993, Bundgaard *et al.* 1996, Janot *et al.* 1996).

The 5-year relative survival rate of Finnish tongue cancer patients was 46% for men and 58% for women in 1985-1994 (Dickman *et al.* 1999). The survival rates are strongly dependent on the TNM stage (International Union Against Cancer, 1987) of the tumour at the time of diagnosis. There is, however, a group of small stage I tongue carcinomas which behave in an unexpectedly aggressive manner. No indisputable prognostic factors for aggressive stage I tumours have been found. Studies on the role of various demographic, clinical and histopathological prognostic factors in early and late stage tumours separately are scarce.

The incidence of cancer of the tongue has also increased in Finland. Thus, the possible changes in patient and tumour characteristics should be recognised. It is extremely important to detect cancer of the tongue at an early stage. Since patient delay is difficult to influence on, the role of the physician/dentist involved should be studied. Furthermore, various known prognostic factors should be evaluated in early and late stage cancers of the tongue separately, to detect the early stage cancers which require aggressive initial therapy. In this work, trends in incidence and patient and tumour characteristics of cancer of the tongue are described. Also, the early detection of tongue cancer in primary care is

studied. The trends in the relative survival rates of Finnish patients with cancer of the tongue are described. The relative survival rate reflects the relative risk of the patient to die from the disease compared to the general population, being thus more informative than the disease-specific survival rate. Finally, various known prognostic factors of the cancer are evaluated in early and late stage cancers of the tongue separately.

2 Review of the literature

2.1 Incidence of cancer of the tongue

The data on the incidence of oral cancer, including cancer of the tongue, are most commonly obtained from population-based cancer registries (Møller 1989, Muir *et al.* 1992, Östman *et al.* 1995, Macfarlane *et al.* 1996). The data provided by the Survival, Epidemiology, and End Results (SEER) program are commonly used in incidence studies conducted in the United States (Davis & Severson 1987, Swango 1996). The SEER program consists of 11 population-based cancer registries and three supplemental registries covering approximately 14% of the United States population (Surveillance, Epidemiology, and End Results 2000).

Oral cancer is the fourth most common cancer in men and the eighth most common cancer in women globally. Overall, cancer of the oral cavity is the fifth commonest cancer in the world (Parkin *et al.* 1993). Approximately 85% of oral cancers are squamous cell carcinomas (SCC) (World Health Organization 1997). Cancer of the tongue is the most common type of oral SCC, accounting for 30-40% of intraoral carcinomas (Møller 1989, Regezi & Sciubba 1993). The highest incidence rates of cancer of the tongue in men are seen in certain parts of India, France and Brazil, being 7.4-9.4 per 100,000 person-years. The lowest incidence rates are found in Northern Europe, where the incidence varies between 0.4 to 1.0 per 100,000 person-years and in some Eastern European countries, in which the incidence rate in men is 1.0 per 100,000 person-years or lower. Furthermore, Japan and China have low incidence rates of cancer of the tongue. (Muir *et al.* 1987). The incidence rates of cancer of the tongue are generally lower in women than in men. The incidence rates in women are highest in India, being 3.4 cases per 100,000 person years in certain parts of the country (Muir *et al.* 1987). Furthermore, the incidence is higher among black than white men in the United States (Swango 1996). In Finland, the incidence of cancer of the tongue was 1.2 per 100,000 person-years in men and 0.8 per 100,000 person-years in women in the period 1990-1994 (Finnish Cancer Registry 2000).

2.1.1 Risk factors for cancer of the tongue

Several risk factors for oral SCC have been reported in the literature. Tobacco is probably the best-known risk factor for oral cancers, including cancer of the tongue. It has been stated that tobacco smoking is responsible for a vast majority of all oral cancers around the world (for a review, see Boyle *et al.* 1995). It has further been noted that the type of tobacco smoked has a role in carcinogenesis. Especially tobacco rich with tar and tobacco-specific nitrosamines increases the risk of oral cancers (for a review, see Boyle *et al.* 1995, Chhabra *et al.* 1996). Furthermore, the duration rather than the intensity of smoking has been found to be an important risk factor for head and neck SCCs (Lewin *et al.* 1998). The role of tobacco in the pathogenesis is largely unknown. However, it has been suggested that the use of tobacco impairs the DNA repair mechanism (Jin *et al.* 1997).

It has also been noted that various alcoholic beverages are associated with an increased risk of oral cancer. It seems that the amount of alcohol consumed and the duration of alcohol use have a more important role in the carcinogenesis of oral cancer than any specific composition of the beverage. Thus, it seems probable that a common ingredient of alcohol beverages is responsible for the increased risk for oral cancers, although pure ethanol itself has not been shown to be carcinogenic. (for a review, see Wight & Ogden 1998). In the literature, several possible mechanisms of how alcohol might influence the development of oral cancer have been presented. For example, it has been stated that alcohol may disturb the DNA repair mechanism and increase the penetration of carcinogens by increasing the permeability of oral mucosa (for a review, see Wight & Ogden 1998).

It is also known that cigarette smoking and heavy use of alcohol together have a synergistic effect on the aetiology of oral SCC (Lewin *et al.* 1998), and the risk of developing cancer of the oral cavity is tobacco and alcohol dose-dependent (Bundgaard *et al.* 1995, Lewin *et al.* 1998). It has been shown, that the penetration of nitrosornicotine into the oral mucosa is enhanced by ethanol (Squier *et al.* 1986).

The effect of tobacco and alcohol on the aetiology of cancer of the tongue, however, is somewhat contradictory. It has been noted that tobacco smokers and heavy drinkers have a greater risk to develop cancer of the floor of the mouth than cancer of the tongue (Franceschi *et al.* 1992, Jovanovic *et al.* 1993, Barasch *et al.* 1994). Furthermore, Bundgaard *et al.* (1994) studied oral SCC among non-users of tobacco and alcohol. They discovered that 43% of the oral cancers in non-users were located on the tongue, whereas the proportion of cancers of the tongue among users of tobacco and alcohol was 28%. This probable resistance towards alcohol and tobacco has been partly explained by the high mobility of the tongue (Franceschi *et al.* 1992).

Smokeless tobacco (snuff) has been considered a risk factor for cancer of the tongue, especially among young men in the United States (Depue 1986, Davis & Severson 1987). However, in Sweden, where the usage of snuff is considerably more common than in the United States, the incidence rates of cancers of the tongue and oral cavity are not particularly high. Furthermore, a population-based study by Lewin *et al.* (1998) revealed no increase in the relative risk (RR) for oral SCC among Swedish snuff users compared to non-users. The differences in the results may be due to differences in the composition

of smokeless tobacco in Sweden and the United States. (Davis & Severson 1987, Lewin *et al.* 1998). Swedish snuff contains less nitrosamines and nicotine than the snuff used in the United States (Merne 2000).

Based on the current literature, it seems that tobacco and alcohol have a role in the aetiology of cancer of the tongue, but the relative importance of these factors is somewhat questionable. Nevertheless, there are various other suggested risk factors for oral SCC. Most of these factors have been studied less in relation to cancer of the tongue.

In the Asian countries, chewing of betel quid or areca nut is the most important risk factor for cancer of the tongue. It is believed that betel quid itself is not carcinogenic, but the tobacco added to the quid is (International Agency for Research on Cancer 1985). Betel quid and areca nut are strongly associated with the development of submucous fibrosis, which is a premalignant disease (for a review, see Johnson 1991).

Dietary habits also appear to be associated with the risk of cancer of the tongue. It has been noted that regular use of green vegetables, carrots, fresh fruits and whole-grain products decreases the risk of cancer of the tongue. (Franceschi *et al.* 1992). Vitamins A, C and E and betacarotene are believed to have a protective influence against oral cancers (Boyle *et al.* 1995).

Local irritation of the tongue is considered a risk factor for cancer. Ill-fitting dentures that cause sores appear to be associated with an increased risk, as is also poor oral hygiene. (Velly *et al.* 1998). Use of mouthwashes containing large amounts of alcohol is speculated to be another risk factor for oral cancer (Winn *et al.* 1991).

Occupational factors may play a small role in the development of oral SCC. Elevated incidence rates have been found among workers exposed to asbestos, mineral fibres and other substances (Boyle *et al.* 1995). In a Finnish study, however, no statistically significant risks for cancer of the tongue were found in any occupational group (Pukkala *et al.* 1994).

SCC of the oral cavity does not cluster in families (Goldstein *et al.* 1994). However, a significantly elevated risk for head and neck cancers was found among persons who had a first-degree relative with cancer. If the relative had head and neck cancer, the risk was even greater. (Foulkes *et al.* 1995). Furthermore, it has been concluded that a family history of upper aerodigestive tract carcinoma is associated with multiple occurrence of upper aerodigestive tract carcinomas (Morita *et al.* 1998). As mentioned earlier, there are differences in the incidence of oral cancer between races (Swango 1996). In a study done among Israeli Jews, ethnic background was related to the prevalence of oral cancer (Gorsky *et al.* 1994).

Numerous studies have been done on the role of viruses in the development of oral SCC. Human papilloma virus (HPV), especially types 16 and 18, is considered to play a role in cancer development (Syrjänen 1997). It has been noted that the HPV detection rate is particularly high among betel quid chewers (Balaram *et al.* 1995). There are, however, contradictory data on the role of HPV, and the rate of detecting the virus in head and neck SCC varies from 0% to 100%, depending on the study (Zeuss *et al.* 1991, Snijders *et al.* 1992). HPV has also been found in the oral mucosa of healthy individuals (Maitland *et al.* 1987). No studies have been done on the prevalence of HPV detection in large series of tongue cancer patients.

Herpes simplex virus (HSV) has also been studied as a risk factor for oral SCC. There is contradictory information about the role of HSV in carcinogenesis, as HSV has been

detected in healthy mucosa as well (Cox *et al.* 1993). The same is true of the Epstein-Barr virus: the virus could not be detected in a single case of head and neck carcinomas (Atula *et al.* 1997), whereas in another study EBV was found in 25% of head and neck cancers (Tyan *et al.* 1993). The controversy in the role of viruses in oral carcinogenesis might partly be explained by the heterogeneous patient populations and the differences between the detection methods used. Also, the “hit and run“ mechanism, whereby the virus might cause genetic damage and then disappear may be responsible for the controversial results (for a review, see Galloway & McDougall 1983).

Fungal infection caused by *Candida albicans* is suggested to be an aetiological factor for oral cancer. There is a debate as to whether it is a risk factor or merely a secondary opportunistic invader. (for a review, see Krogh 1990 & Johnson 1991). Nevertheless, it has been proven that *C. albicans* is able to promote neoplastic changes (O’Grady & Reade 1992). The role of *C. albicans* in the aetiology of especially cancer of the tongue is unknown.

It has been found that patients with the human immunodeficiency virus (HIV) have an increased risk of developing cancers (Bernstein & Hamilton 1993). Nevertheless, no increase in the incidence of oral SCC has been seen the HIV-positive persons (Monfardini *et al.* 1989). Drug-induced immunosuppression has also been considered a risk factor for oral cancer (for a review, see Johnson 1991). Furthermore, if a transplant patient has been exposed to tobacco and alcohol before transplantation, the risk for oropharyngeal SCC may increase (Duvoux *et al.* 1999).

2.1.2 Trends in incidence

In Scandinavia, the incidence of oral cancer has been increasing among both sexes since the late 1960s (Møller 1989, Mork & Glattre 1998). The increase in incidence has occurred mainly in rural areas (Mork & Glattre 1998). In the United States, the male-to-female ratio decreased significantly from the late 1930s to the mid-1980s, even though the incidence rates of cancers of the oral cavity remained lower in women than in men (Chen *et al.* 1991).

The trend in the incidence of cancer of the tongue has been similar to that of other oral cancers in Europe and in the United States. As a matter of fact, a Norwegian study indicated that the increase in the incidence of oral cancers was mainly caused by the increase of cancer of the tongue, especially among the young age groups (Mork & Glattre 1998). In Finland, the age-standardised incidence rate of cancer of the tongue among men increased from 0.8 per 100,000 person-years in 1965-1969 to 1.2 per 100,000 person-years in 1990-1994. Among women the rates were 0.5 per 100,000 person-years and 0.8 per 100,000 person-years, respectively. (Finnish Cancer Registry 2000).

It has been concluded by several authors that, in men, the incidence of cancer of the tongue steadily decreased from the 1940s to around the 1970s, when it started to increase in Europe and in the United States (Davis & Severson 1987, Møller 1989, Macfarlane *et al.* 1992, Swango 1996). The increase was especially obvious in the age groups of under 40 years (Davis & Severson 1987, Swango 1996). In Scotland the age-standardised incidence of cancer of the tongue increased from 0.9 to 3.0 per 100,000 person-years in

men aged 35-64 years between 1960-1964 and 1985-1989, while at the same time the incidence decreased in old men aged 70 years or over (Macfarlane *et al.* 1992). No such trend in incidence has been seen in women (Davis & Severson 1987, Macfarlane *et al.* 1992). In a Swedish study the age-standardised incidence rates of cancer of the tongue increased between the time periods 1960-1969 and 1980-1989 from 0.9 to 1.2 per 100,000 person-years. The increase was especially seen among men. The male-to-female ratio increased from 1.3:1 to 1.9:1 during the study period. (Östman *et al.* 1995). In Denmark, however, the incidence of cancer of the tongue doubled in both sexes between 1958 and 1985 (Møller 1989). Furthermore, a more recent American study revealed that the incidence of cancer of the tongue had increased between 1973 and 1987 in all race and sex groups, except in black females (Swango 1996). Despite the fact that the incidence rates have increased especially among young men, the age-specific incidence rates are highest among persons aged 60 years and over (Macfarlane *et al.* 1992, Swango 1996).

The increased consumption of alcohol during the past decades has been blamed for the increase seen in the incidence of cancer of the tongue (Møller 1989, Macfarlane *et al.* 1992). Furthermore, the incidence of oral cancer has increased especially in the most seriously deprived areas, where the use of tobacco and alcohol is common (Macfarlane *et al.* 1996). However, Macfarlane *et al.* (1996) found that even though the prevalence of smoking declined in the United Kingdom, causing a decrease in the incidence of lung cancer, the incidence of oral cancer increased. Similarly, in Finland the incidence of cancer of the lung has declined over the past decades (Finnish Foundation for Cancer Research 1989). This shows that there must be other aetiological factors besides tobacco and alcohol responsible for the increased incidence.

2.2 Detection of cancer of the tongue

There are no studies on the delay in the diagnosis cancer of the tongue specifically. In previous works, the study populations have consisted of more heterogeneous patient groups suffering from oral SCC. About half of oral cancers are larger than 4 cm in diameter at the time of diagnosis (Wildt *et al.* 1995). The patient's main primary reason for seeking medical advice has been reported to be pain at the tumour site, followed by a lump or swelling and an ulcer (Guggenheimer *et al.* 1989).

As the incidence of oral cancer has increased over the past decades in Europe and the United States, there has been discussion in the literature on whether to screen for oral cancers or not. Screening for oral cancer by visual inspection is simple, inexpensive and does not cause discomfort for the patient. However, there is no evidence about the effectiveness of the screening programs for oral cancer. (for a review, see Rodrigues *et al.* 1998). Only a very recent work proved the effectiveness of the screening. Sankaranarayanan *et al.* (2000) reported early findings from a community-based, cluster-randomised, controlled oral cancer screening program from India. They found that, among the patients diagnosed in the screening program, 76% had a localised disease (stage I-II) compared to 13% among the patients in the control group. Furthermore, the 3-

year mortality rates were lower among the patients detected in the screening program (15%) compared to the control group (56%).

The delay in cancer diagnosis has not received much attention, and there are only a few studies available concerning the delay in the diagnosis of oral cancers. The delay is generally divided into patient delay and professional delay.

2.2.1 Patient delay

Patient delay has mainly been studied in selected or hospital-based materials. The data on the length of the delay have been obtained by either interviewing the patients or through a questionnaire. (Hackett *et al.* 1973, Guggenheimer *et al.* 1989, Dimitroulis *et al.* 1992, Jovanovic *et al.* 1992, Wildt *et al.* 1995). As the studies have been done retrospectively, the patients have been aware of their cancer diagnosis before the interview or the filling in of the questionnaire. Thus, knowledge of the diagnosis may have effected a recall bias in the data.

It has been concluded that the delay in the diagnosis of oral SCC is mainly caused by the patient (Dimitroulis *et al.* 1992, Jovanovic *et al.* 1992, Wildt *et al.* 1995). Furthermore, patients with oral cancer are more likely to delay seeking medical advice compared to patients suffering from cancers at other sites (Hackett *et al.* 1973). This is thought to be due to the asymptomatic nature of oral cancer at its early stage and the incapability of the patients to distinguish between ominous and innocuous symptoms in the oral cavity (Guggenheimer *et al.* 1989). It has been suspected, however, that most patients are aware of the tumour in the oral cavity before making an appointment with a physician/dentist, but it is the patient's attitude towards personal health that causes the delay. There is a group of patients who deliberately deny the existence of the tumour or simply ignore it, and thus do not seek medical advice until at a late stage of the disease. Furthermore, patients who accept the possible malignant nature of their disease seek for medical advice sooner than those who deny or ignore it. Persons who tend to worry about their health are more likely to deny the cancer symptoms and postpone making the appointment. This has been thought to be the reason why public health information campaigns have had only a minor influence on patient delay, which has remained constant through decades. (Hackett *et al.* 1973, Wildt *et al.* 1995).

The mean patient delay varies from three to five months in oral cancers (Dimitroulis *et al.* 1992, Jovanovic *et al.* 1992, Wildt *et al.* 1995). Neither age nor sex has been found to correlate with the delay (Guggenheimer *et al.* 1989, Wildt *et al.* 1995). In an earlier study, low socio-economic status was found to be related to prolonged delay (Hackett *et al.* 1973), but a more recent work revealed no such correlation (Guggenheimer *et al.* 1989). Elwood & Gallagher (1985) concluded that regular dental check-ups and low alcohol consumption were related to early diagnosis of oral carcinoma. Nevertheless, Jovanovic *et al.* (1992) and Wildt *et al.* (1995) did not find the patient's dental status or regular dental check-ups to be related to the length of patient delay. Furthermore, Guggenheimer *et al.* (1989) did not find any association between abundant alcohol intake and long patient delay.

According to the literature, there is no correlation between the length of patient delay and the TNM stage of the tumour at the time of diagnosis (Dimitroulis *et al.* 1992, Jovanovic *et al.* 1992, Wildt *et al.* 1995). Dimitroulis *et al.* (1992) found that patients with stage T2-3 tumours had a longer delay in seeking medical advice than patients with T4 tumours. This has led to a speculation that tumours detected at an early stage grow more slowly than those detected at a more advanced stage. Thus, it seems that it is the growing rate of the tumour rather than the duration of symptoms that contributes to the patient delay. (Dimitroulis *et al.* 1992, Wildt *et al.* 1995).

2.2.2 Professional delay

Most of the earlier studies have been done on hospital-based or otherwise selected patient series (Scully *et al.* 1986, Dimitroulis *et al.* 1992, Jovanovic *et al.* 1992, Kowalski *et al.* 1994, Wildt *et al.* 1995, Allison *et al.* 1998a, Allison *et al.* 1998b). In the studies by Scully *et al.* (1986) and Dimitroulis *et al.* (1992), the data were gathered from the referral letters. Allison *et al.* (1998a) obtained the data on the first visit to a health professional by interviewing the patients, but the information was validated by checking it against the primary care files in 30 (out of 188) randomly selected cases.

The mean professional delay in oral SCC has been reported to be between one and two months (Dimitroulis *et al.* 1992, Jovanovic *et al.* 1992, Wildt *et al.* 1995). A Danish study showed the professional delay to be over two months in 20% of the cases of oral SCC, and in a Canadian study, 15% of the cases had a professional delay of over three months (Wildt *et al.* 1995, Allison *et al.* 1998a). According to Wildt *et al.* (1995), women and elderly patients often had a prolonged professional delay in the diagnosis, whereas according to Allison *et al.* (1998b) the patient's old age (over 65 years) shortened the professional delay. A Brazilian study indicated that black and mulatto oral cancer patients had a significant risk of being left untreated compared to white patients, resulting in a poorer prognosis among coloured people (Franco *et al.* 1993). Moreover, it has been concluded that not only are the racial minorities less likely to use medical services (for a review, see Facione *et al.* 1993), but when they do, the decisions concerning their treatment are unfavourably related to their race (Geiger 1996).

Contrary to patient delay, a correlation between professional delay and prognosis has been found. Kowalski *et al.* (1994) found that a professional delay for over a month predicted a late stage disease in oral and oropharyngeal carcinomas. According to Allison *et al.* (1998a), there was a significant risk for a late stage disease among oral cancer patients when the professional delay exceeded three months. Nevertheless, there is also a study where no correlation between the length of the professional delay and the stage of the disease was found (Wildt *et al.* 1995).

According to the earlier studies, about 40% of the patients made their initial appointment with a dental practitioner (Scully *et al.* 1986, Dimitroulis *et al.* 1992, Wildt *et al.* 1995). There are no differences in professional delay between dentists and general practitioners (Wildt *et al.* 1995). It seems, however, that patients with late stage cancers of the oral cavity seek medical advice from a physician rather than a dentist, which may

lead to physicians tending to emphasise the urgency of the case in a referral letter compared to dentists (Scully *et al.* 1986, Dimitroulis *et al.* 1992).

Interestingly, physicians and dentists have different approaches to treating misdiagnosed oral lesions. Physicians tend to use drug therapy by prescribing antibiotics and antifungal drugs, whereas dentists use more mechanical approaches, i.e., denture adjustments or tooth extractions. (Scully *et al.* 1986, Dimitroulis *et al.* 1992). Even though a majority of oral cancer patients are referred to a referral centre within a reasonable time frame, an interesting observation was made by Dimitroulis *et al.* (1992): only 16% of the referral letters mentioned the possibility of a malignant lesion.

In cases with small and less visible oral and pharyngeal tumours, the professional delay is significantly longer than in larger tumours (Wildt *et al.* 1995, Allison *et al.* 1998b). Kowalski *et al.* (1994) found that patients with tumours at less visible sites have a significant risk to be diagnosed at a late stage. Furthermore, patients with other than oral symptoms present at the initial visit to the physician/dentist have a significant risk for a prolonged professional delay. The doctors who are aware of the patient's prior diagnosis tend to focus on this disease rather than the oral symptoms, which are usually quite innocuous at the early stage of the cancer. (Allison *et al.* 1998b).

2.3 Prognosis of cancer of the tongue

A limited number of studies have been done on the survival of patients with cancer of the tongue alone, and a few have been done on a larger patient series with oral cancers. There are previous studies on both population-based (Silverman & Gorsky 1990, Levi *et al.* 1992, Nyman *et al.* 1993, Macfarlane *et al.* 1996, Mork & Glatre 1998, Berrino *et al.* 1998, Dickman *et al.* 1999) and hospital-based (Franceschi *et al.* 1993, Kirita *et al.* 1994) patient series. Furthermore, any comparison of the previous works is complicated, as at least two different variables are generally used to measure the patient outcome in tongue and oral cavity cancers. They are the relative survival rate and the disease-specific survival rate. The relative survival rate is the ratio of the observed survival of a given group of patients to the survival the group would have experienced based on the life-table of the population from which they were diagnosed (Everitt 1995). Thus, the relative survival rate is the ratio of observed to expected rates, and it reveals the increased risk of death caused by the disease within a specified time-period after the cancer diagnosis. The observed survival rate is the proportion of patients alive after a certain period following the cancer diagnosis. In the disease-specific survival rate, deaths due to other causes than the disease studied are excluded.

The average 5-year relative survival rate of cancer of the tongue in Europe was 37% in men and 50% in women in 1985-1989. It has been shown that cancers at the tip or the lateral side of the tongue as well as those on the ventral surface have better survival rates than those at other sub-sites. (Berrino *et al.* 1998). In Finland, the 5-year relative survival rate of cancer of the tongue was 46% in men and 58% in women in 1985-1994 (Dickman *et al.* 1999).

The overall 5-year observed survival rate of tongue cancer varies within 30-60% (Silverman & Gorsky 1990, Franceschi *et al.* 1993, Nyman *et al.* 1993). Approximately

25-35% of tongue cancer patients develop a locoregional recurrence. Seventy-five percent of the recurrences emerge within a year after the treatment of the primary cancer. (Franceschi *et al.* 1993, Kirita *et al.* 1994). According to Kirita *et al.* (1994) the 5-year survival rate was 45% among the tongue cancer patients who developed a recurrence during the follow-up, while for the patients without a recurrence the rate was 74.

2.3.1 Trends in prognosis

The 5-year relative survival rates in Finnish patients with cancer of the tongue were 46% in men and 58% in women in 1985-1994. Only slight improvements were seen in the relative survival rates during the study period 1955-1994. The stage of the disease at the time of diagnosis had a significant effect on the relative survival rates. The survival rates were lower among men throughout the study period. Even when the cases were stratified by the stage, lower survival rates were observed in men. (Dickman *et al.* 1999). In a Norwegian study, the five-year relative survival rate of oral cancer patients improved from 37% to 45% in men and from 37% to 53% in women during the past 40 years (Mork & Glattre 1998). The improvement in survival was seen especially among the younger age groups under 55 years of age. The five-year relative survival rate was the same among the three studied subtypes of oral cancer: the tongue, the floor of the mouth and the oral cavity.

Relative survival rates have also been calculated by combining oral and pharyngeal carcinomas, to achieve larger study populations (Levi *et al.* 1992, Macfarlane *et al.* 1996). In Switzerland, the 5-year relative survival rates of these cancers have remained almost the same in both sexes. The 5-year relative survival rates were 35% in 1974-1978 and 30% in 1979-1983 among men and 50% and 44% among women, respectively. However, the 5-year relative survival rate decreased in patients under 60 years of age from 46% in 1974-1978 to 34% in 1979-1983, while no clear trend in the rate was seen in older patients. (Levi *et al.* 1992). Similar figures were obtained in a Scottish study, where the 5-year relative survival rate decreased from 47% in 1968-1972 to 39% in 1983-1987 in patients aged under 65 years, but improved somewhat among the older patients, their rates being 34% and 38%, respectively. In the total series, the 5-year relative survival rate remained almost unchanged, being 41% in 1968-1972 and 39% in 1983-1987. (Macfarlane *et al.* 1996). Furthermore, Macfarlane *et al.* (1996) observed that the 5-year relative survival rates of oral and pharyngeal cancers were lowest in the most deprived areas. They concluded that the more prevalent use of tobacco and alcohol in these areas might be reflected in the survival rates. The results cannot be directly compared to the studies done on cancers of the tongue or oral cavity, as the prognosis of head and neck cancers varies widely (Tobias *et al.* 1994).

Franceschi *et al.* (1993) concluded that, in a hospital-based patient series, the disease-specific 5-year survival rates improved in both early and late stage cancers of the tongue between 1967-1978 and 1978-1987. The survival rate improved from 75% to 82% in stage I-II tumours and from 37% to 49% in stage III-IV tumours. Nevertheless, the stage distribution remained unchanged throughout the study period. (Franceschi *et al.* 1993). Similarly, Mork & Glattre (1998) concluded that the stage distribution of cancer of the

tongue has remained the same over the past 40 years in Norway, but the relative survival rates of all oral cancers have improved both in men and in women. Thus, it seems that it is the more effective treatment that improves the survival, as noted by Franceschi *et al.* (1993).

2.4 Prognostic factors of cancer of the tongue

As mentioned earlier, some 30% of tongue cancer patients develop a locoregional recurrence. A vast majority of the recurrences emerge within a year after the initial cancer treatment. (Franceschi *et al.* 1993, Kirita *et al.* 1994). The most common site for metastasis is the ipsilateral neck nodes. Cervical lymph node metastases are found to be associated with significantly poorer survival than recurrence at the primary site. (Nathanson & Ågren 1989).

Several studies have been done on the prognostic factors of SCC of the tongue and oral cavity. The majority of previous studies have been done on selected or hospital-based patient series. Although there are a few population-based studies on the subject (Atula *et al.* 1996, Mork & Glatre 1998), only a few works have been conducted prospectively (Hedge *et al.* 1998), while the rest have been done retrospectively. The prognostic factors can be divided into demographic, clinical and histopathological factors.

2.4.1 Demographic factors

The role of age as a prognostic factor in cancer of the tongue is controversial. Sarkaria & Harari (1994) investigated six patients with cancer of the tongue aged under 40 years and performed a review of literature. They concluded that young patients with cancer of the tongue have a higher locoregional failure rate and a lower disease-specific survival rate than older patients. Friedlander *et al.* (1998) investigated disease-specific survival and locoregional failure in patients with cancer of the tongue under 40 years of age and matched older patients. They did not discover differences in disease-specific survival rates between the groups, but both local and regional recurrence rates were higher among patients under 40 years of age. Siegelmann-Danieli *et al.* (1998) did not find any difference in the recurrence-free rate or disease-specific or overall survival between patients aged 45 years or less and older patients with cancer of the tongue. In a Finnish study, the overall 5-year survival rate was as good as 71% among young tongue cancer patients aged under 40 years (Atula *et al.* 1996). Moreover, in a study by McGregor *et al.* (1983), better survival rates were obtained for young (aged under 40 years) patients with cancer of the tongue and oral cavity compared to older ones. In Norway, the relative survival rates of oral cancer patients improved over time in the young age groups (Mork & Glatre 1998). Even when the material was analysed separately for patients with localised and regional disease and stratified by age groups, the improvement in survival was noted. In this particular study, cancer of the tongue accounted for 79% of the oral cancers among patients under 35 years of age.

The relative survival rates of tongue cancer are lower in men than in women throughout Europe. In a collaborative work done by 17 cancer registries around Europe, the average age-adjusted 5-year relative survival rates of cancer of the tongue were 37% in men and 50% in women in 1985-1994. (Berrino *et al.* 1998). In Finland, too, the relative survival rate of cancer of the tongue is lower in men than in women. The age-adjusted 5-year relative survival rate was 45% in men and 58% in women in 1985-1994. The difference in rates was observed even in the patient group with localised disease. (Dickman *et al.* 1999). A Brazilian study showed that men with oral cancer had significantly lower disease-free survival rates than women. However, this was most probably due to the slightly higher proportion of advanced (stage III-IV) disease among men. No difference in survival rates between the sexes was seen when patients with cancer of the tongue were analysed separately. (Franco *et al.* 1993).

Interestingly, in a study done specifically on patients with cancer of the tongue, better disease-specific survival rates were found among smokers and users of alcohol compared to non-users (Siegelmann-Danieli *et al.* 1998). Generally, a low socio-economic status and a deprived place of residence have been discovered to predict a poor prognosis in patients with oral cancer (Macfarlane *et al.* 1996). Furthermore, smoking and heavy use of alcohol are independently related to a poor prognosis of oral cancer patients. It has been speculated that patients who live in a deprived area, have a low socio-economic status and smoke and use excessive amounts of alcohol do not seek medical advice until at a late stage of the disease and thus have a poor prognosis.

2.4.2 Clinical factors

The TNM stage of the tumour (International Union Against Cancer 1987) is the most important prognostic factor of SCC of the tongue. The treatment of cancer of the tongue is largely dictated by the TNM stage of the tumour. There is, however, a subgroup of small stage I tumours which behave in an unexpectedly aggressive manner, which indicates that there are other significant prognostic factors involved in tumour behaviour. In 30-40% of the cases with TNM stage I-II cancer of the tongue, cervical metastases occur after the primary treatment (Nathanson & Ågren 1989, Asakage *et al.* 1998).

The growth type and appearance of the tumour have a prognostic value. Patients with exophytic and more superficial tumours have a better prognosis than those with ulcerative and more invasive type of tumours (Asakage *et al.* 1998).

A clinical parameter not taken into account in TNM staging is tumour thickness. It has been proven by several authors that the thickness of the primary tumour predicts the regional recurrence of the disease and the disease-free survival of the patients (Brown *et al.* 1989, Nathanson & Ågren 1989, Asakage *et al.* 1998). Tumour thickness is measured from the surface of mucosa to the deepest portion of the tumour, regardless of whether the tumour is exophytic or invasive (Brown *et al.* 1989, Asakage *et al.* 1998). According to Nathanson & Ågren (1989), cancers of the tongue over 10 mm in thickness have a significantly poorer prognosis than thinner ones, whereas Asakage *et al.* (1998) found that tongue cancers over 4 mm thick have a poorer prognosis. It has been proposed that

clinically local and small (TNM stages I-II) tumours should be treated in a more aggressive manner if the thickness of the tumour exceeds a certain cut-off value (Nathanson & Ågren 1989, Asakage *et al.* 1998).

Compared to the TNM stage, tumour thickness is relatively difficult to measure retrospectively, and the quality of the samples available varies. The sections have been made in different angles or only from the periphery of the tumour. The biopsies are usually superficial and rarely include the deepest part of the tumour. The thickness of the tumour should therefore be measured from the surgical preparation block during the operation, which is a rather difficult and time-consuming. According to Asakage *et al.* (1998), however, ultrasonography might be accurate enough for measuring tumour thickness.

2.4.3 Histopathological factors

Several histopathological prognostic factors of SCC of the tongue and oral cavity have been studied (Table 1).

Table 1. A list of the best-known histopathological prognostic factors of tongue cancer.

Prognostic factors	
Apoptosis*	p53 protein*
Cell cycle inhibiting proteins ¹	Nuclear DNA content ²
Grade*	Perineural invasion*
HPV, HSV-1 or EBV infection*	Proliferative markers Ki67 and AgNOR ³
Inflammatory response*	Tumour angiogenesis*
Malignancy score*	

*The variable is reviewed below.

¹Bova *et al.* 1999, Mineta *et al.* 1999

²Högmo *et al.* 1999, for a review, see Baretton *et al.* 1995

³Piffkø *et al.* 1997, Xie *et al.* 1999

2.4.3.1 Grade

The grading of squamous cell carcinomas of the oral cavity is based on the International Histological Classification of Tumours (World Health Organization 1997). The grading system was introduced by Broders as early as the 1920s. The system takes into account the degree of keratinisation, cellular and nuclear polymorphism and mitotic activity of the tumour.

In general, the system categorises tumours according to the proportion of tumour tissue resembling normal squamous epithelium. The grades are well-differentiated (Grade 1), moderately differentiated (Grade 2) and poorly differentiated (Grade 3). In well-differentiated tumours, the histological and cytological features closely resemble the normal squamous epithelial lining the oral mucosa. Keratinisation of cells is a common feature, and few mitotic figures are seen. Atypical mitoses or multinucleated epithelial cells are extremely rare. The nuclear and cellular pleomorphism seen is minimal. Moderately differentiated tumours have less keratinisation and more nuclear and cellular pleomorphism compared to well-differentiated tumours. There are also more mitotic figures, and few of them are abnormal in shape. Compared to well-differentiated tumours, intercellular bridges are less distinct. Poorly differentiated tumours resemble only slightly the normal stratified squamous epithelium histologically. Keratinisation and intercellular bridges are rarely seen. Mitotic activity is frequent and atypical mitoses can easily be found. Cellular and nuclear pleomorphism is obvious and multinucleated cells may be seen frequently. Well and moderately differentiated tumours can be considered as low-grade and poorly differentiated tumours as high-grade tumours. (World Health Organization, 1997).

The majority of tongue cancers are low-grade tumours. Despite the widespread use of the method, there are several studies on oral SCC in which the WHO grade has not been found to have a prognostic value (Rasgon *et al.* 1989, Gluckman *et al.* 1997, Piffkò *et al.* 1997).

2.4.3.2 Malignancy score

Numerous different grading systems of heterogeneous prognostic value have been introduced after Broder's classification (for a review, see Anneroth *et al.* 1987). Jakobsson *et al.* (1973) introduced a new grading system for head and neck SCC, which was based on eight different factors: tumour structure, differentiation (according to keratinisation), nuclear polymorphism, mitoses, mode of invasion, stage of invasion, vascular invasion and cellular response. The system has proven to have significant prognostic value in SCC of the tongue (Odell *et al.* 1994, Högmo *et al.* 1999). Anneroth *et al.* (1987) further developed Jakobsson's grading, the main change being that the factors were studied from the less differentiated parts of the tumour. Bryne *et al.* (1989) introduced a new malignancy grading system based on the studies by Jakobsson and Anneroth. According to Bryne, five features (degree of keratinisation, nuclear polymorphism, number of mitoses, pattern of invasion and leukocyte infiltration) are studied from the deepest invasive margin of the tumour. Bryne's malignancy grading has been proven to have a significant prognostic value in cancers of the oral cavity (Bryne *et al.* 1989, Gluckman *et al.* 1997, Piffkò *et al.* 1997). The Jakobsson grading system has also been modified by others. The modification by Lund *et al.* (1975) has been used in the literature, and it has proven to have prognostic value in oral SCC (Bundgaard *et al.* 1996).

Furthermore, there are works in which individual factors of Jakobsson's or Bryne's grading system have been studied separately. It has been noted that the pattern of invasion

at the deep invasive front of the tumour has the most significant influence on prognosis (Crissman *et al.* 1984, Odell *et al.* 1994, Bundgaard *et al.* 1996).

2.4.3.3 Tumour angiogenesis

A growing tumour is supplied by neovascularisation. Furthermore, neovascularisation permits tumour cells to be in contact with the vascular bed of the host. In breast cancers, an association between vascular density and tumour aggressivity was found in the early 1990s (Weidner *et al.* 1991). The finding encouraged researchers to study tumour angiogenesis in head and neck SCCs as well. The microvessel density of the tumour is usually determined from the periphery of the tumour at the “hot spot” site (i.e., the highest microvessel density area). An association between high microvessel density and metastases has been found in small T1 cancers of the tongue (Shpitzer *et al.* 1996) as well as in cancers of the oral cavity and head and neck region (Gasparini *et al.* 1993, Williams *et al.* 1994). There are, however, several studies with opposite results (Gleich *et al.* 1996, Janot *et al.* 1996, Gleich *et al.* 1997, Högmo *et al.* 1999). Interestingly, in a majority of the studies done in more homogenous patient groups, including cancers of only the tongue or only the oral cavity, tumour angiogenesis has not proved to have any prognostic value (Leedy *et al.* 1994, Gleich *et al.* 1996, Gleich *et al.* 1997, Gluckman *et al.* 1997, Högmo *et al.* 1999). Gleich *et al.* (1997) concluded that, due to the high vascularity of the site, tumours of the oral cavity are probably less dependent on neovascularisation than tumours at other sites. They also speculated that genetic alterations in tumours may allow tumour growth in an anoxic environment, where no neovascularisation is needed. In the case of larger tumours, the evaluation of angiogenesis is very difficult, since it is impossible to evaluate the entire tumour, and highly vascular areas may thus be missed. Furthermore, the staining techniques (Factor VIIIaAg and CD-31 or 34) do not distinguish a new vessel from an old one, and thus neovascularisation cannot be accurately measured by counting stained microvessels. (Gleich *et al.* 1997).

Due to the problems in evaluating tumour angiogenesis, the vascular endothelial growth factor (VEGF) released from tumour cells, has been studied. Maeda *et al.* (1998) found that oral cancer patients with VEGF-positive stained tumours had significantly poorer overall survival rates than VEGF-negative tumours. There was, however, no association between VEGF positivity and neck node metastases. Furthermore, VEGF did not significantly correlate with the TNM stage of the tumour. (Maeda *et al.* 1998).

2.4.3.4 Inflammatory response

A heavy inflammatory infiltrate at the periphery of the tumour correlates with a better prognosis of patients with cancer of the head and neck (Mohit-Tabatabai *et al.* 1986, Rasgon *et al.* 1989, Magnano *et al.* 1995). Sarioglu *et al.* (1994) came up with similar results in terms of cancer of the tongue specifically. The result, however, was not statistically significant. Controversial data also exist. Horiuchi *et al.* (1993) did not find a

correlation between the infiltrate and the prognosis of patients with SCC of the oral cavity.

In a majority of the previous studies, the total number of inflammatory cells is summed up and the infiltration is considered heavy, moderate or mild. Lymphocytic cells have also been studied individually. Heavy eosinophilic infiltration has been related to a poor prognosis in patients with cancer of the oral cavity (Horiuchi *et al.* 1993).

Overall, the prognostic role of the inflammatory response in SCC of the oral cavity has been studied less often. It is assumed that lymphocytic infiltration is a host response against the tumour. The mechanism of the immune system in carcinogenesis, however, is largely unknown.

2.4.3.5 Perineural invasion

Perineural invasion has been considered a negative prognostic factor in SCC of the oral cavity, (Brown *et al.* 1989, Lydiatt *et al.* 1993) as well as in SCC of the head and neck in general (Magnano *et al.* 1999). Brown *et al.* (1989) observed that perineural invasion predicted a significantly poorer prognosis in patients with cancer of tongue and the floor of mouth. On the contrary, in a more recent work by Asakage *et al.* (1998), perineural invasion had no significant prognostic value in cancer of the tongue, even though there was a slight tendency towards a better prognosis among the cases without perineural invasion. However, only four of the 44 tumours studied showed signs of perineural invasion. Detection of perineural invasion is difficult, as a single histological slide represents only a very small part of the tumour.

2.4.3.6 Apoptosis

Apoptosis is a genetically regulated active process in which changes in cellular architecture occur, resulting in self-destruction of the cell (Kerr *et al.* 1994). Apoptosis is complementary to mitosis in regulating cell populations in both physiological and pathological conditions (Kerr *et al.* 1972). The bcl-2 (B-cell leukaemia 2) family proteins are the most important regulators of apoptosis. There are apoptosis-inhibiting and apoptosis-promoting members in the family. Bcl-2 is the most widely studied apoptosis-inhibiting protein, whereas bax (bcl-2 homologous antagonist x) is the most widely studied apoptosis-promoting member of the family. (for a review, see Soini *et al.* 1998). In previous studies, the apoptotic index (i.e., the proportion of apoptotic cells of all tumour cells) has usually been determined. Furthermore, the existence of bcl-2 and bax has been studied.

Apoptosis has been studied extensively in breast, endometrial, gastrointestinal, lung, prostate, thyroid and urogenital carcinomas, but less intensively in SCC of the head and neck. Yao *et al.* (1999) studied bcl-2 expression in SCC of the tongue. They noted that the bcl-2 protein had a prognostic value: frequent expression of bcl-2 was associated with a decrease in the apoptotic index. Nevertheless, they did not find an association between the expression of bcl-2 and the prognosis of the patients with cancer of the tongue. In a

Finnish study of patients with cancer of the tongue under 40 years of age, no association between bcl-2 and the stage and grade of the tumour was found. Furthermore, the expression of bcl-2 did not have an effect on patient survival. (Atula *et al.* 1996). In a Norwegian study, a low apoptotic index was discovered to correlate with a poor prognosis, while abundant bax expression was related to a good prognosis in patients with cancer of the tongue (Xie *et al.* 1999). The authors further combined the proliferative and apoptotic parameters, which appeared to have an even stronger prognostic value. The apoptotic factor score was subtracted from the proliferative factor score, and results over zero predicted a poor prognosis.

There are, however, also contradictory data on the role of apoptosis in the prognosis of SCC of the head and neck. Jäckel *et al.* (1999) found that the frequency of apoptotic cells significantly correlated with high mitotic activity, a high malignancy grade of the tumour and disease progression in laryngeal carcinomas. This indicates that extensive spontaneous apoptosis balances the high rate of mitosis and thus reflects the growth rate of the tumour. Furthermore, no correlation between bcl-2, bax or the bcl-2-to-bax ratio and the rate of apoptosis was observed by Jäckel *et al.* (1999). Similarly, Eerola (1999) failed to discover a correlation between the presence of bcl-2 and apoptosis in small and large-cell lung carcinomas. Furthermore, high apoptotic activity in large-cell lung carcinoma indicated a poor prognosis (Eerola 1999).

It has been noted that the ratio between the apoptotic and mitotic indexes is higher in dysplasia than in carcinomas, which indicates that apoptosis is “hidden“ because of the cell proliferation in invasive lesions (for a review, see Soini *et al.* 1998).

2.4.3.7 p53

In cancer research, p53 is the most thoroughly studied gene. In general, the role of wild-type p53 is to maintain genomic integrity. When cells are exposed to ionizing radiation or other mutagenic events, p53 mediates cell cycle arrest or apoptosis. (for a review, see Moll & Schramm 1998). Furthermore, the normally functioning p53 gene has been found to determine the willingness of tumour cells to undergo apoptosis after radiation or chemotherapy (Lowe *et al.* 1994).

The most common pattern of disturbing p53 function is a mutation in the coding sequence. The majority of mutations are reported to map in the exons 4 to 8 (Sakai & Tsuchida 1992, Field *et al.* 1994). The mutated p53 protein is found in 25-60% of the oral SCCs, depending on the study (Chiba *et al.* 1996, Piffkò *et al.* 1998). Furthermore, the function of p53 may be blocked by viral interaction: proteins of certain tumour viruses are able to bind to p53 and thus to disturb its function (Szekely *et al.* 1993, Foster *et al.* 1994). These events cause inactivation of p53, which allows uncontrolled distribution of cells, leading ultimately to the formation of a malignant tumour. Inactivation of the gene further causes accumulation of p53. Thus, both expression of the mutated p53 protein and overexpression of the p53 protein assessed by immunohistochemical staining (IHC) have been studied as prognostic factors in SCCs of the head and neck including cancer of the tongue. The wild-type p53 is not usually detectable in healthy cells, as it decomposes rapidly in normal conditions.

Atula *et al.* (1996) found that the excessive expression of p53 assessed by IHC was associated with a large size of the tumour in tongue cancer patients aged under 40 years. In the study, mutated p53 did not correlate with tumour size, grade or neck node status at the time of diagnosis. However, they did discover that, in moderately and poorly differentiated tumours the expression of p53 mutations tended to be related with poor prognosis (Atula *et al.* 1996). In a more recent work, a positive association between the overexpression of p53 detected by IHC and regional recurrence of the disease was seen in small, stage I cancers of the tongue (Högmo *et al.* 1999). In a study by Leedy *et al.* (1994), no correlation between the expression of p53 assessed by IHC and the occurrence of neck node metastases was observed in small (T1-2) cancers of the tongue. Interestingly, Sauter *et al.* (1992) noted that overexpression of p53 correlates with a better prognosis in patients with SCC of base of the tongue.

p53 has not been found to be an indisputable prognostic factor in SCC of the oral cavity, either. Gulckman *et al.* (1997) detected immunohistochemically p53 in aggressive and non-aggressive oral cavity SCCs, and no association between tumour behaviour and the expression of p53 was observed. Piffkò *et al.* (1998) reported significantly more p53-positive cells in the invasive front of the tumour than in the other parts. Therefore, they analysed the expression of p53 from the invasive front of SCC of the oral cavity, using immunohistochemical and molecular genetic techniques to achieve maximum sensitivity. The alterations of p53 did not prove to have prognostic value. In studies on more heterogeneous patient groups, including SCC of the head and neck, a clear relationship between both the expression of p53 assessed by IHC (Gasparini *et al.* 1993) and the presence of mutated p53 (Hegde *et al.* 1998) with poor prognosis has been reported. In a multivariate analysis, however, the expression of p53 assessed by IHC did not prove to have any prognostic value in head and neck carcinomas, either (Gasparini *et al.* 1993).

It has been shown in animal models that p53 mutations may permit tumour growth in hypoxic areas (Graeber *et al.* 1996). Maeda *et al.* (1998) did not find a significant correlation between vascular endothelial growth factor (VEGF) and mutated p53, even though a trend towards a positive correlation was seen. Intense immunoreactivity of VEGF is frequently observed in the most necrotic areas of the tumour, which could indicate that hypoxia might induce VEGF expression (Maeda *et al.* 1998). According to a few studies, a high microvessel density of the tumour and overexpression of p53 correlate. However, contradictory data on the overexpression of p53 assessed by IHC and the presence of mutated p53 in correlation with VEGF exist. Gasparini *et al.* (1993) found a positive correlation between immunohistochemically detected expression of p53 and VEGF in SCC of the head and neck, whereas Hedge *et al.* (1998) reported an inverse relationship between mutated p53 and microvessel density.

As mentioned earlier, bcl-2 inhibits apoptosis and p53 participates in the induction of apoptosis. Yao *et al.* (1999) studied the correlation between bcl-2 and p53 immunoreactivity and discovered that these parameters combined had a significant prognostic value in SCCs of the tongue: when both bcl-2 and p53 were detected in the lesion, the patient's prognosis was poor.

It is known that a gene (E6) of the human papilloma virus (HPV) encodes a protein which binds to p53. This binding results in p53 degradation (Scheffner *et al.* 1990). It has been speculated that this may have a role in the transforming ability of the "high-risk group" human papilloma viruses (Chiba *et al.* 1996). This is why the prognostic role of

p53 has been studied together with the expression of HPV. Chiba *et al.* (1996) did not find any correlation between patient or tumour-related prognostic factors and the presence of p53 mutations or HPV in patients with SCC of the oral cavity. They did, however, note that p53 mutation-negative and HPV-negative cases had a poorer prognosis than p53 mutation-positive and HPV-positive patients. Furthermore, they observed that the p53 mutation/HPV-positive cases did not significantly differ as to any of the studied patient or tumour-related factors from the p53 mutation/HPV-negative cases. (Chiba *et al.* 1996). Rietdorf *et al.* (1997) studied p53 and HPV in SCC of the head and neck: in 40% of the HPV-positive cases there was a mutated p53 protein present. Nevertheless, neither the mutated p53 nor the presence of HPV had a prognostic value according to this study.

The mutated p53 protein has also been detected in normal oral mucosa of oral SCC patients as well as in healthy individuals (Ogden *et al.* 1997). No significant correlation between the development of primary or secondary malignant tumours and the presence of the mutated p53 has been found.

2.4.3.8 Viruses

In cervical carcinomas, the absence of HPV correlates with a poorer prognosis (Higgins *et al.* 1991). Yet, HPV has not been proven to have an indisputable effect on the prognosis of patients with carcinoma of the upper aerodigestive tract (Chiba *et al.* 1996, Rietdorf *et al.* 1997). Nevertheless, Pintos *et al.* (1999) noted that, in a series with SCC of the head and neck, the outcome was slightly better in the patients with HPV DNA than in those without the virus. The result, however, was not statistically significant.

The prognostic value of other viruses in oral SCC has been studied even less. In a recent work, oral SCC patients with Epstein-Barr virus (EBV) infection had a good prognosis, suggesting a favourable prognostic role of EBV (Kobayashi *et al.* 1999). Contrary to EBV, the herpes simplex virus-1 (HSV-1) has been found to predict a poor prognosis in oral SCC patients (Shillitoe *et al.* 1986). No relationship between the presence of cytomegalovirus and the prognosis of oral SCC has been observed (Shillitoe *et al.* 1986). The prognostic value of these viruses has not been studied in cancer of the tongue specifically.

3 Aims of the study

The aims of the present survey were:

1. To determine the trends in the incidence and survival of cancer of the mobile tongue in Finland over the past 40 years.
2. To determine whether there have been any changes in the patient and tumour characteristics of cancer of the mobile tongue over the past 20 years in a geographically defined area of Northern Finland.
3. To evaluate the detection of tongue cancer in primary health care and its effect on patient outcome.
4. To evaluate the relative importance of various known prognostic factors in a population-based sample of patients with cancer of the mobile tongue. Specifically, to determine the prognostic factors of early stage tumours, in order to be able to recognise the patients who may require more aggressive initial therapy.

4 Patients and methods

4.1 Study design

This study was a retrospective population-based descriptive cohort analysis. The cohort constituted the patients with cancer of the mobile tongue in 1953-1994 in Finland and in 1974-1994 in Northern Finland. The incidence of cancer of the mobile tongue and the survival of the patients were studied nationwide. The patients diagnosed in a geographically defined area of Northern Finland were analysed in more detail. When the detection and prognostic factors of tongue cancer were determined, the study design was an unexperimental comparative study.

4.2 Subjects

4.2.1 Incidence and survival of cancer of the tongue in Finland

The study included all patients with a first diagnosis of primary cancer of the mobile tongue (ICD-7, code 141, except 141.0 base of tongue) in Finland between 1953 and 1994. The data were obtained from the Finnish Cancer Registry, which was founded in 1952. All hospitals, pathological and cytological laboratories and practitioners in Finland are required to report to the Cancer Registry every new cancer case that comes to their attention. Furthermore, the Registry obtains information on deaths from cancer and on deaths of cancer patients from causes other than cancer. The Registry files can be considered practically complete for cancer patients in Finland, also the follow-up of the patients is complete (Teppo *et al.* 1994).

According to the Cancer Registry a total of 1504 patients with cancer of the mobile tongue were diagnosed in Finland in 1953-1994. The data on these patients were obtained from the registry. To protect the anonymity of the patients, the file did not contain the patients' names, dates of birth or personal identification numbers.

4.2.2 Patient and tumour characteristics (II), early detection (III) and prognostic factors (IV) of cancer of the tongue

The health care system in Finland is based on a general health insurance scheme, which allows equal access to medical and hospital services for everyone. The communal dental care, however, is provided only in part of the Finnish communities. Furthermore, dental care is supported by the state only to patients born in or after the year 1956 as in 1999.

All patients with cancer of the mobile tongue (ICD 9, codes 141.1-141.9) in the two northernmost provinces of Finland (Oulu and Lapland) were included in the study. The Oulu University Hospital, founded in 1974, is the only tertiary referral centre in the area, and thus almost all patients with cancer of the tongue are treated there. The patients with cancer of the mobile tongue diagnosed in 1974-1994 were identified from the surgical, radiotherapy and discharge registers of the Oulu University Hospital. A total of 108 new cases with squamous cell carcinoma of the mobile tongue were found. Three cases were excluded from the studies II and III because of insufficient clinical data. Eight cases were further excluded from study IV because of poor quality of the sections, leaving 97 patients for the histopathological analysis. During the study, several tissue specimens unfortunately wore out, and only 55 samples were available for the final analysis (apoptosis).

4.3 Methods

4.3.1 Incidence and survival of cancer of the tongue in Finland (I)

Data on the patients' age (under 65 years vs. 65 + years), sex, place of residence at the time of diagnosis, date of diagnosis and tumour stage were drawn from the Finnish Cancer Registry. Tumour stage had been recorded on the basis of clinical examinations supplemented by pathologists' reports and classified into three categories: localised (cancer confined to the mobile tongue regardless of size), regional (cancer extending to the regional lymph nodes), and distant (cancer spreading beyond the tongue or involving tissues beyond those immediately draining the tongue). Advanced cases of unknown width were classified as distant. Tumour stage could not be classified in 187 (12%) patients.

4.3.2 Patient and tumour characteristics (I) and early detection (III) of cancer of the tongue

The patients' tertiary care files were retrospectively reviewed by the author, and data on demographic and clinical characteristics were abstracted (I, III). The following patient-related factors were recorded: patients' age (years), sex, socio-economic status (employer, self-employed worker, higher level employee vs. lower-level employee, manual worker,

other) (United Nations 1978), place of residence (urban vs. rural) (Statistics Finland 1993), duration of symptoms in months, smoking habits (current or ex smoker vs. non-smoker) and alcohol consumption (no, light or moderate vs. heavy). Alcohol consumption was regarded as heavy if the patient had been diagnosed as an alcoholic or he/she drank alcoholic beverages daily. (I, III)

The following tumour-related factors were collected from the hospital files: the date of histologically verified diagnosis of cancer, tumour size (mm), tumour location in the tongue (margin, upper surface, lower surface, diffuse), tumour grade according to WHO (1997), local tumour spreading outside the tongue (buccal mucosa, gingival region, mandible, floor of mouth, base of the tongue or vallecula), neck node status of the patients (determined by clinical inspection, ultrasonography or computer tomography), and TNM stage of the tumour (International Union Against Cancer, 1987) (I, III). Furthermore, a malignancy score introduced by Bryne et al. (1992) was determined from the pre-treatment biopsies of the cases (III).

The source of referral was determined from the patient's referral letter (III). The author sent a letter to the primary care physicians and dentists who had referred the patients to tertiary care centre. In the case of an unknown referral source, a letter was sent to the primary care unit, which could have been consulted by the patient prior the diagnosis of cancer of the tongue. In the letter, the medical and dental primary care records concerning the visits prior to the cancer diagnosis were requested. The primary care patient files were missing or were not sent to us in 18 (17%) cases, leaving 87 patients. Ten cases referred from primary care were further excluded because of a premalignant lesion in the tongue, which underwent a cancerous change during the hospital follow-up and two cases discovered incidentally at the tertiary centre. The remaining 75 patients were included in the study. (III).

From the medical and dental records received, data on visits prior to the referral were reviewed by the author (III). Possible delay in diagnosis was divided into two parts: patient delay and professional delay. Patient delay was defined as the interval between the perception of the first symptoms and the initial professional evaluation, which was the first medical visit after the onset of symptoms regardless of the reason the patient had made the appointment for. Professional delay was determined as the interval between the initial consultation and the final histologically verified diagnosis of cancer (the date drawn from tertiary care files). Total delay was the sum of patient and professional delays. The delays were determined in months. (III).

Furthermore, the following factors were collected from the primary care files: primary reason for the initial visit to a physician/dentist (pain in the tongue, other specific symptom in the tongue, unspecific symptom in the oral cavity or other), tumour appearance (exophytic vs. indurated, ulcerative, crater), data on examination at the initial visit (inspection of the mouth, palpation of the tongue and biopsy of the tumour), suspected diagnosis, data on the medical professional (physician vs. dentist), primary care unit (communal vs. private), data on living condition (lives at home independently vs. lives with relatives or in an institution) and whether the patient was a smoker or non-smoker. (III)

4.3.3 Prognostic factors of cancer of the tongue (IV)

The data on patient and tumour related prognostic factors were gathered from patients' tertiary care files as described in a previous chapter. Of the histopathological prognostic factors studied, the WHO grade of the tumour (well differentiated, moderately differentiated or poorly differentiated) was reviewed from the tertiary care files of the patient. The other histopathological factors were determined from the 97 pre-treatment biopsy sections obtained. The histological sections were analysed in a blinded manner without knowledge of the patient outcome by two senior pathologists. The scores determined were based on an agreement between the two pathologists. The following factors were determined from the sections: malignancy score according to Bryne et al. (1992), tumour angiogenesis, inflammatory cell count, nerve invasion, apoptosis, overexpression of p53 protein and expression of human papilloma virus (HPV) DNA.

4.3.3.1 Malignancy score

The malignancy score of the tumours was determined from hematoxylin-eosine (H&E) stained sections according to the method introduced by Bryne et al. (1992). A score from 1 to 4 was given to five morphological features: degree of keratinisation, nuclear polymorphism, number of mitoses, pattern of invasion and lymphoplasmacytic infiltration (Table 2). The total score (5-20) was summed up into a malignancy score. In the analysis, the patients were divided into three groups according to the malignancy score: 5-10 points, 11-15 points and 16-20 points.

Table 2. Malignancy grading according to Bryne et al. (1992)

Characteristics	Score
Degree of keratinisation	
highly keratinised	1
moderately keratinised	2
minimally keratinised	3
no keratinisation	4
Nuclear polymorphism	
slight nuclear polymorphism	1
moderate nuclear polymorphism	2
clear nuclear polymorphism	3
excessive nuclear polymorphism	4
Number of mitoses	
0-1	1
2-3	2
4-5	3
5+	4
Pattern of invasion	
pushing, well-recognised infiltrating borders	1
infiltrating, but solid cords and/or strands	2
small groups of infiltrating cells, number of cells over 15	3
marked and widespread cellular disorder in small groups of cells, number of cells under 15	4
Lymphoplasmacytic infiltration	
heavy	1
moderate	2
slight	3
none	4

4.3.3.2 Tumour angiogenesis

Tumour angiogenesis was determined from sections immunohistochemically stained for factor VIII (Dako, Glostrup, Denmark) and CD-34 (Novo Laboratories, Bagsvaerd, Denmark). The method used was similar to that in the study of Leedy et al. (1994). A secondary antibodies used were biotinylated swine immunoglobulins to rabbit immunoglobulins, Dako E353, dilution 1:200/PBS for factor VIII staining and biotinylated rabbit immunoglobulins to mouse immunoglobulins, Dako E354, dilution 1:300/PBS for CD-34 staining. The microvessels, excluding only single cells, were

counted in ten high-power field areas (objective x40; diameter of the field 400 µm). The mean value of the vessels in ten random fields within the tumour was counted. For the statistical analysis, the values were divided into three groups according to the quartiles of the means.

4.3.3.3 *Inflammatory response*

Inflammatory cells (polymorphonuclear, neutrophilic and eosinophilic leukocytes, lymphocytes and plasma cells) were analysed on the margin of the tumour (objective x 40, diameter of the field 400 µm) from H&E-stained sections. The amount of the total inflammatory infiltrate was categorised as light (+), moderate (++) or heavy (+++).

4.3.3.4 *Perineural invasion*

Nerve invasion was determined by using S-100 stained sections (Dako, Glostrup, Denmark). Nerve invasion was considered positive if there were clearly recognisable SCC cells in any of the nerves present in the biopsy section.

4.3.3.5 *Apoptosis*

To determine tumour apoptosis, the 3'-end labelling of apoptotic cell DNA was performed using the ApopTag[®] *in situ* apoptosis detection kit (Oncor, Gaithersburg, MD) following the manufacturer's instructions with a few modifications, as described by Soini et al. (1996). The cells were considered apoptotic if the whole nuclear area labelled positively. To estimate the apoptotic index, the number of tumour cells per high-power field area was divided with the sum of apoptotic cells and bodies in the high-power field. The apoptotic index was counted from the ten high-power fields (objective x40; diameter of the field 400 µm) and statistically analysed with a similar method as microvessels.

4.3.3.6 *p53*

The expression p53 protein was analysed from immunohistochemically stained sections using a Vectastain[®] ABC kit (Vector-laboratories, Burlingame, CA). The method used was similar to that described by Soini & Pääkkö (1996). The immunohistochemical staining was done using the polyclonal rabbit anti-human p53 antibody CM-1 (Vectastain[®], Vector Laboratories, Burlingame, USA) diluted 1:1000 followed by a biotinylated secondary anti-rabbit antibody and the avidin-biotin-peroxidase complex (Vectastain[®], Elite ABC Kit). Nonimmune rabbit (CM-1) serum was substituted for negative control stainings. The p53 immunostained cells were counted. The immunostaining was evaluated on the basis of the nuclear immunoreaction and recorded as negative (-), weakly positive (+) or strongly positive (++) .

4.3.3.7 HPV

The existence of human papilloma virus DNA (HPV 6, 11, 16, 18, 31 and 33 subtypes) in the sections was studied with *in situ* hybridisation and polymerase chain reaction (PCR). The *in situ* hybridisation was performed using non-radioactively labelled DNA probes and a commercially available hybridisation kit (Biohit, Helsinki, Finland) following the manufacturer's instructions. The method used was similar to that described by Soini et al. (1996). Human papilloma virus was also detected by PCR, using the HPV-consensus primers MY 09 and MY 11 and β -actin by 5'sense and 3'antisense primers according to Ponte et al. (1984).

4.3.4 Statistical methods

The incidence rates of cancer of the tongue in Finland were standardised to the "world standard population" (Doll *et al.* 1966) and expressed per 100,000 person-years. (I). Survival was measured as five- and 15-year relative survival rates. The expected survival rates were calculated from population life-tables (supplied by Statistics Finland) compiled according to age, sex and year of diagnosis (five-year calendar period) using the Relative Survival Analysis program (Hakulinen & Abeywickrama 1985). Age-standardised truncated incidence rates and actuarial relative survival curves were computed for two age categories (<65 and 65+ years) and sex and tumour stage (obtained from the Finnish Cancer Registry). To analyse the trends in incidence and survival in Finland, the 42-year study period (1953-1994) was divided into six seven-year calendar periods (1953-59, 1960-66, 1967-73, 1974-80, 1981-87 and 1988-94) for practical reasons. The period-specific incidence and survival rates were further analysed according to age, sex and tumour stage. (I)

The annual age-specific incidence rates of cancer of the mobile tongue in Northern Finland were calculated using the corresponding mid-year population figures as denominators in 15-year age groups (II). For a comparison of annual incidences, age-standardised rates were calculated with a direct method, using weights from the age distribution of the population in the area as in 1984. To analyse the trends in incidence and the demographic and clinical variables, the 21-year study period (1974-1994) was divided into three seven-year calendar periods (1974-80, 1981-87 and 1988-94) for practical reasons. (II)

To analyse the effect of professional delay on patient survival, the study population was divided into groups based on the referral pattern as follows: 1) patients correctly referred for further examinations at the initial visit, 2) patients not referred but scheduled for a follow-up visit and 3) patients neither referred, nor controlled (III). The differences in the categorical variables between the groups were analysed with chi-square test. For the continuous variables, the groups were compared with the Kruskal-Wallis test. The relative hazard of death and the 95% confidence intervals (CI) adjusted by the main known prognostic factors (TNM stage of the tumour, age, sex, and histological malignancy grading by Bryne et al. 1992) were estimated by Cox's regression model. The summary statistics for the categorical data was presented as numbers and percentages.

The continuous data were presented by using the median and range. Disease-specific mean survival times and their standard errors were determined with the Kaplan-Meier method and compared with the log rank test. In the analysis, all the p-values less than 0.05 were considered as statistically significant. (III)

To evaluate the prevalence of patients with cancer of the tongue of all the visits in primary care, the number of primary care physicians and overall patient visits in primary care in the year 1996 in the provinces of Oulu and Lapland were obtained from the Finnish Medical Association. (III)

The inter-relationship between the various prognostic factors was assessed with the chi-square method (IV). The disease-specific mean survival and recurrence-free times and their 95% confidence intervals (CI) were calculated with the Kaplan-Meier method and compared by the log rank test (III, IV). The disease-specific 75th percentile survival times and their ranges were also determined according to the prognostic factors. The values were compared with Breslow's test. To study further the prognostic effect of demographic and histopathologic factors, a stratified analysis was performed for early (Stages I-II) and late (Stages III-IV) stage tumours separately. In all the analyses, p-values of 0.05 or less were considered statistically significant. (IV)

5 RESULTS

5.1 Incidence of cancer of the tongue

5.1.1 Finland

The age-standardised incidence rate of cancer of the mobile tongue in Finland was 0.6 per 100,000 person-years in 1953-1994. In men the incidence was 0.7 and in women 0.5 per 100,000 person-years. The incidence increased by age. The age-standardised incidence rate in men decreased after the mid-1960s, but started to increase again in the early 1970s (Figure 1). In women, respectively, the incidence decreased slightly towards the end of the 1980s, after which it increased.

5.1.2 Northern Finland

The age-standardised incidence rate of cancer of the mobile tongue per 100,000 person-years was 0.9 in men and 1.1 in women in Northern Finland during 1974-1994. Over the study period, the incidence increased from 0.6 per 100,000 person-years (1974-1980) to 1.0 (1988-1994) in men and from 0.7 to 1.4 in women (Figure 2).

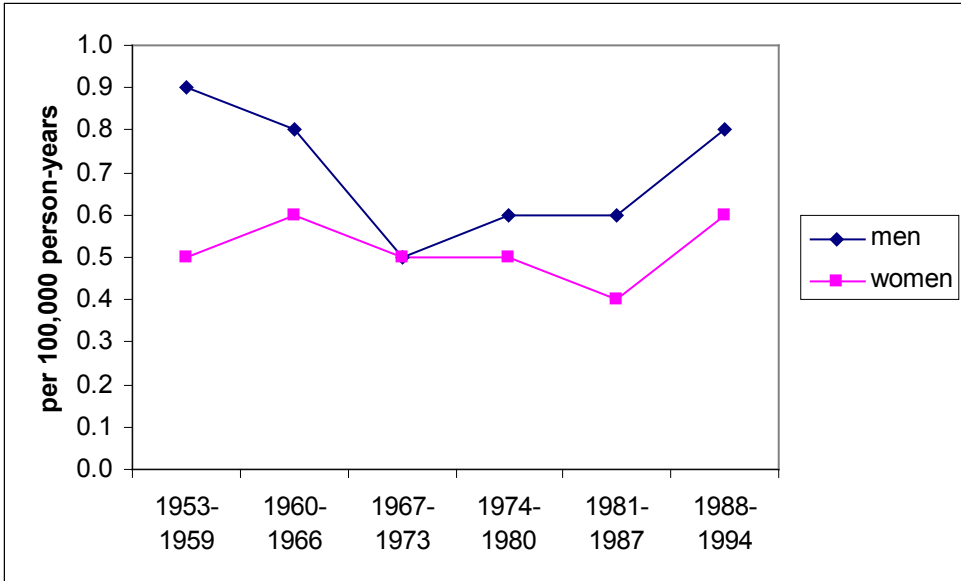


Fig. 1. Age-standardised incidence rates (per 100,000 person-years) of cancer of the tongue in Finland 1953-1994.

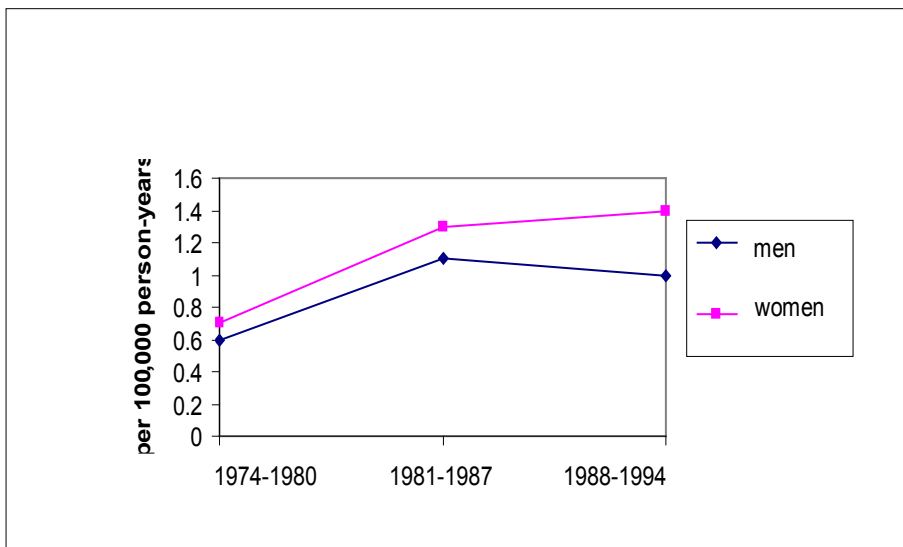


Fig. 2. Age-standardised incidence rates (per 100,000 person-years) of cancer of the tongue in Northern Finland 1974-1994.

5.2 Patient and tumour characteristics

Patient characteristics of the study are presented in Table 3. The proportion of female patients increased from 48% in 1953-1959 to 55% in 1988-1994 nationwide. In the same time, the proportion of old patients aged 65 years or over, increased from 38% to 53%.

Over the 21-year study period (1974-1994), the median age of patients in Northern Finland remained unchanged. The sex distribution also remained the same, being slightly female dominated throughout the study period. (Table 4). Furthermore, there was no change in the domicile (urban vs. rural) of the patients (Statistics Finland, 1993). The socio-economic status (United Nations, 1978) of the patients seemed to change during the study period: in 1974-1980, all the diagnosed patients had a low socio-economic status, while in the latest period (1988-1994) the proportion was 84%.

Table 3. Patient characteristics of cancer of the tongue in a nationwide material of 1504 patients in 1953-1994 and in a population-based sample of 105 patients in Northern Finland in 1974-1994.

Patient characteristics	n	(%)
<i>Finland (1953-1994)</i>	<i>1504</i>	
Number of patients		
Men	720	(48)
Women	784	(52)
Age		
0-64 years	755	(50)
≥65 years	749	(50)
<i>Northern Finland (1974-1994)</i>	<i>105</i>	
Number of patients		
Men	45	(43)
Women	60	(57)
Age		
0-64 years	57	(54)
≥65 years	48	(46)
Urban domicile	68	(65)
Low socio-economic status*	78/87	(90)
Smoking*	49/87	(56)
Heavy use of alcohol*	15/68	(22)

*Calculated for those with data available

Table 4. Trends in age-adjusted incidence rate and patient and tumour characteristics of tongue cancer in 1504 patients nationwide (1953-1994) and in 105 patients in Northern Finland (1974-1994).

Subpopulation	Calendar period					
	1953-1959	1960-1966	1967-1973	1974-1980	1981-1987	1988-1994
Finland (n=1504)						
Incidence rate per 100,000 person-years (I) and proportion (%) of cases						
Men I, (%)	0.83 (52)	0.83 (50)	0.52 (44)	0.59 (46)	0.64 (48)	0.76 (45)
Women I, (%)	0.54 (48)	0.56 (50)	0.46 (56)	0.47 (54)	0.40 (52)	0.51 (55)
Patients' age [median, (min, max)]	61 (22, 89)	64 (14, 91)	63 (7, 89)	64 (0, 92)	68 (22, 95)	66 (19, 97)
Tumour stage*						
Patients with localised disease [n, (%)]	139 (67)	157 (67)	125 (65)	129 (56)	160 (60)	186 (50)
Patients with regional disease [n, (%)]	50 (24)	40 (17)	25 (19)	32 (14)	48 (18)	74 (20)
Patients with distant disease [n, (%)]	8 (4)	21 (9)	15 (8)	35 (15)	29 (11)	37 (10)
Patients with unknown stage [n, (%)]	10 (5)	16 (7)	27 (14)	35 (15)	29 (11)	74 (20)
Northern Finland (n=105)						
Patients age [median, (min, max)]				63 (40, 80)	64 (33, 90)	64 (26, 88)
Tumour size, mm [median, (min, max)]				40(10, 60)	30(10, 60)	38 (5, 100)
Tumour stage						
Patients with stage I disease [n, (%)]				2 (12)	5 (12)	7 (15)
Patients with stage II disease [n, (%)]				3 (18)	11 (27)	16 (34)
Patients with stage III disease [n, (%)]				9 (53)	14 (34)	18 (38)
Patients with stage IV disease [n, (%)]				2 (12)	11 (27)	3 (6)
Patients with unknown stage [n, (%)]				1 (6)	-	3 (6)

*Staging according to Finnish Cancer Registry

Table 5. Tumour characteristics of cancer of the tongue among 1504 patients nationwide (1953-1994) and among 105 patients in Northern Finland (1974-1994).

Tumour characteristics	n	(%)
<i>Finland (1953-1994)</i>		
<i>1504</i>		
Tumour stage*		
Localised disease	904	(60)
Regional disease	268	(18)
Distant disease	145	(10)
Unknown	187	(12)
<i>Northern Finland (1974-1994)</i>		
<i>105</i>		
TNM stage of the tumour		
I	14	(13)
II	30	(29)
III	41	(39)
IV	16	(15)
Unknown	4	(4)
Local spread outside the tongue	23	(22)
Tumour location at the tongue		
Marginal	72	(68)
Lower surface	20	(19)
Upper surface	3	(3)
Diffuse	10	(9)

*Stages according to Finnish Cancer Registry

In the nationwide data set, the proportion of localised tumours decreased from 67% in 1953-1959 to 50% in 1988-1994. At the same time the proportion of unknown stages increased from 5% to 20%. (Table 4). The proportion of localised tumours was higher among females (63%) than in males and higher among patients aged under 65 years (62%) than in older patients.

There were no marked changes in the distributions of the TNM stage of the tumours, the local spreading of the tumours or the median tumour size over the 21-year study period in Northern Finland (Table 4).

5.3 Detection of cancer of the tongue

5.3.1 Primary symptoms

Eighteen (24%) patients named pain as the primary reason for seeking medical advice from primary care unit. In 30 (40%) cases, the primary symptom was a specific sign in the tongue, i.e., a painless lump or an ulceration in the tongue. Nine patients had non-specific symptoms in the oral cavity. Sixteen patients had made the initial appointment for a totally unrelated reason. These reasons were, in the order of frequency: fatigue or general weakness, common cold, routine dental examination, blood pressure control, chest pain, installation of a hearing aid, hemoptysis, menopausal problems, rehabilitation control, stomach ache and tension neck. In two cases the primary symptom was unknown. Regardless of the reason the initial medical appointment was made for, all patients mentioned an oral symptom during the visit. A vast majority (81%) of the patients first contacted a medical practitioner, while 14 (19%) contacted a dental practitioner.

5.3.2 Delay in diagnosis

Forty-nine (65%) patients were correctly referred for further examinations at the initial visit. In 12 (16%) cases, the patient was not referred but was scheduled for a follow-up visit, and in 14 (19%) cases the patient was neither referred nor controlled. The overall median professional delay was 0.7 months (range 0.1–18.2) (Figure 3). The delay was significantly longer for the unreferred patients who were left without follow-up compared to those referred immediately ($p < 0.001$). The median patient delay, on the contrary, tended to be shortest for the unreferred and uncontrolled patients.

In 37 (77%) cases referred at the initial visit, the patient's primary symptom was either pain or a specific sign in the tongue. Furthermore, of the 25 patients whose main complaint was either a non-specific tumour symptom or an unrelated symptom, only 10 (40%) were referred at the initial visit. The tumours that remained undiagnosed at the first medical visit tended to be larger, ulcerative, histologically more aggressive and more advanced than those detected immediately. Moreover, the initially misdiagnosed tumours tended to be located more often on the lower or upper surface of the tongue than the ones diagnosed at the initial visit.

At the initial visit, visual inspection of the mouth was done in every case, palpation of the tumour in only 14 (19%) cases and in 11 (15%) the tumour was biopsied. The palpated tumours tended to be referred more often. A benign lesion or an infection was generally suspected in the unreferred patients. There were no differences in the ability to refer patients correctly between physicians and dentists or between communal health care centre and private care practitioners.

Patients with a low socio-economic status and a rural place of domicile and incapable of living independently at home were more likely to go unreferred. Among the unreferred patients, urban domicile was associated with no scheduled follow-up.

5.3.3 Effect on prognosis

The mean disease-specific survival time was significantly longer among the patients referred correctly at the initial visit than among the unreferred patients and shortest among the unreferred uncontrolled patients (Figure 3). The relative hazard of death, adjusted with the main prognostic factors, was 1.4 (95% confidence interval 0.3-6.5) for the unreferred controlled patients and 6.3 (95% confidence interval 1.7-22.9) for the unreferred uncontrolled patients compared to the immediately referred patients.

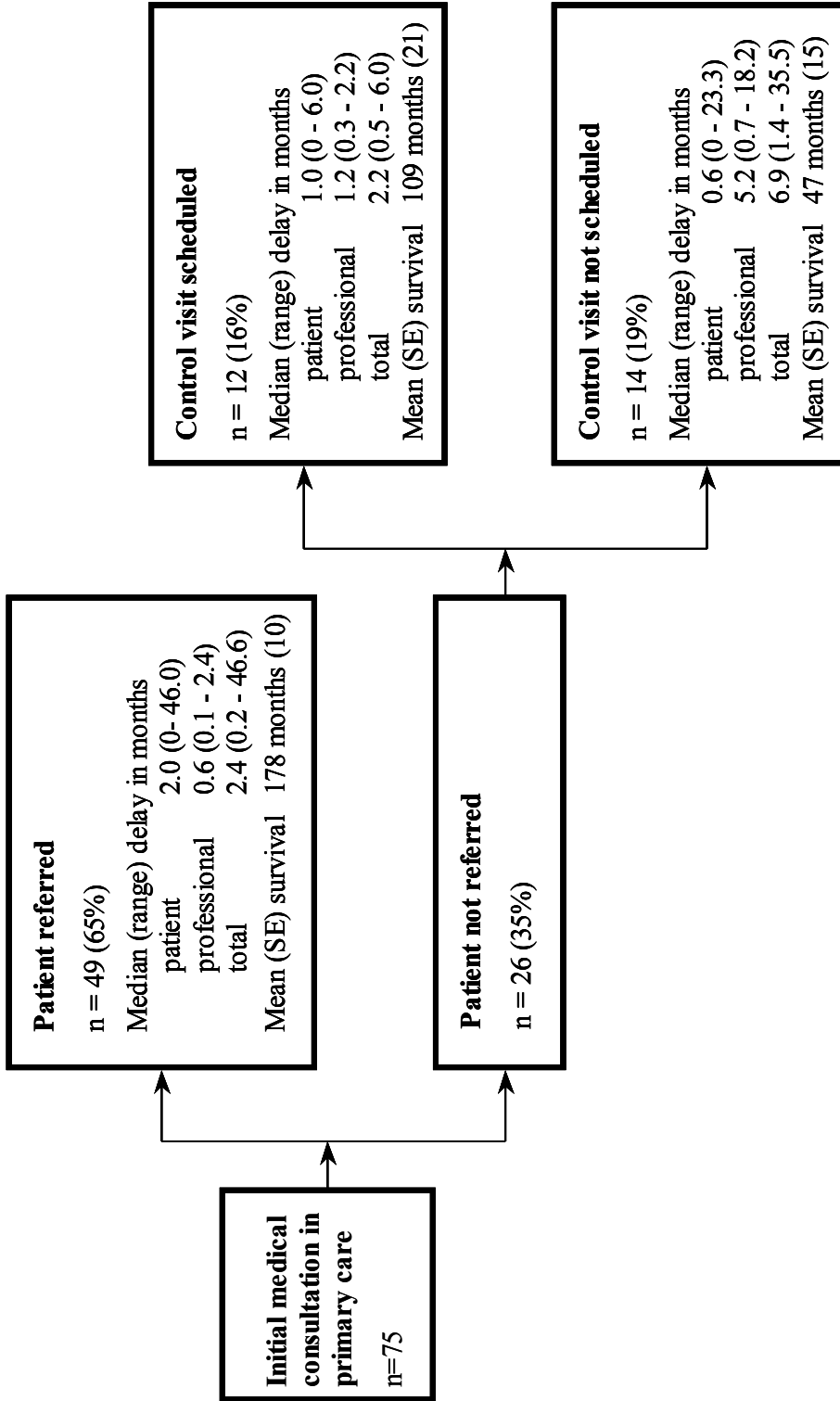


Fig.3 Detection of tongue cancer patients in primary health care in Northern Finland in 1974-1994 (mean survival times are disease-specific)

5.4 Survival of patients with cancer of the tongue

The overall five-year relative survival rate of cancer of the tongue was 49% in 1953-1994. The five-year relative survival rate increased from 40% in 1953-1959 to 58% in 1988-1994. The stage of the tumour at the time of diagnosis had the most significant effect on survival, the overall 5-year relative survival rate being 62% for localised disease, 31% for regional disease and only 5% for distant disease. Over the study period, the relative survival rate increased among patients with localised and particularly among patients with regional disease, but not among those with distant disease (Figure 4). The improvement in survival was seen in both age-groups, but more markedly so among the patients aged 65 years and over. In this group, the 5-year relative survival increased from 27% in 1953-1959 to 61% in 1988-1994. The survival rate increased in both sexes.

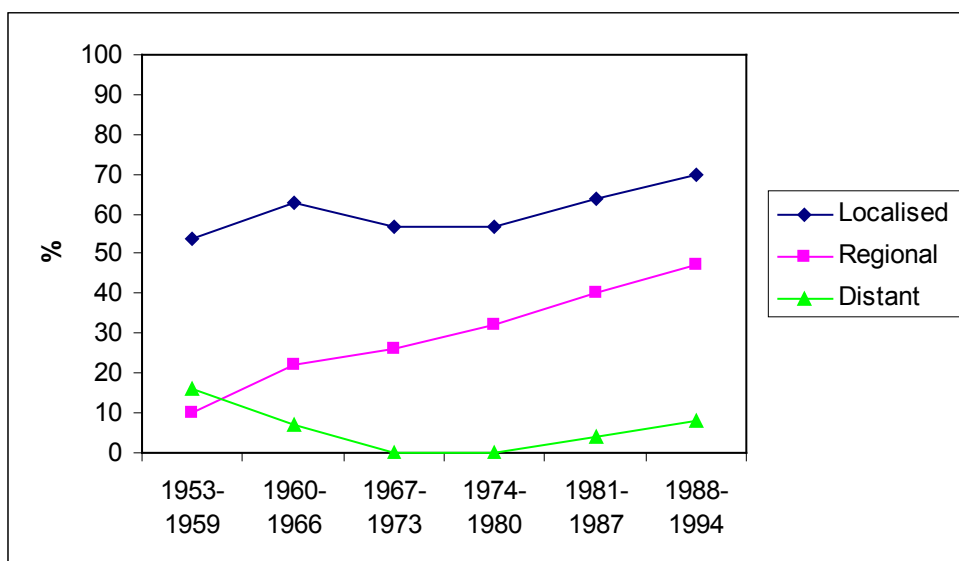


Fig. 4. Relative survival rates of cancer of the tongue according to tumour stage in Finland 1953-1994.

5.5 Prognostic factors

In univariate analysis, old age of the patient (65 + years) and heavy use of alcohol predicted poorer prognosis. None of the other demographic factors studied had a significant effect on survival. The TNM stage and local spread of the tumour were the

tumour-related factors, which had a significant effect on the disease-specific survival time. Metastatic neck nodes present at the time of diagnosis did not have a statistically significant effect on prognosis. None of the histopathological factors had a significant effect on disease-specific survival time. However, a low malignancy score, heavy tumour angiogenesis, a heavy inflammatory response at the most lateral margin of the tumour and strongly positive p53 expression in IHC tended to be related to a better prognosis.

When the interrelationships of the factors were evaluated, male sex, old age, low socio-economic status, smoking and heavy use of alcohol correlated significantly with clinical spreading of the tumour. Furthermore, low tumour angiogenesis, high malignancy score, heavy inflammatory response at the edge of the tumour, heavy apoptosis and p53 not detected by IHC were also found to significantly correlate with tumour spreading. Since several demographic and histopathological prognostic factors were related to the TNM stage of the tumour, the variables were further analysed in early (Stages I-II) and late (Stages III-IV) stage tumours separately.

5.5.1 Early stage tumours

In early stage tumours, older age of the patient, high malignancy score and p53 not detected by IHC significantly shortened the disease-specific survival times (Table 6). Furthermore, there was a tendency for a high apoptotic index and heavy tumour angiogenesis to be related to a better prognosis.

5.5.2 Late stage tumours

In late stage tumours, heavy use of alcohol was significantly related to a poor prognosis (Table 6). Also smoking tended to correlate with a poor prognosis, even though the correlation was not statistically significant. Heavy tumour angiogenesis tended to be related to a better prognosis, as did a moderate or marked inflammatory response at the margin of the tumour.

Table 6. The disease-specific 75th percentile survival times (ST) in months and range according to patient-related and histopathologic prognostic factors in early stage (Stages I-II) and late stage (Stages III-IV) carcinomas in 101 patients with cancer of the tongue (stage was unknown for four patients).

	(n)	Early stage carcinomas ST (range)	p	(n)	Late stage carcinomas ST (range)	p
All patients ^a	(44)	91 (6-91)		(57)	14 (3-43)	
Gender			0.79			0.70
Women	(27)	>60 ^b		(30)	19 (5-43)	
Men	(17)	31 (6-91)		(27)	12 (3-17)	
Age group			0.03			0.62
65 yrs and under	(24)	>60 ^b		(32)	14 (3-22)	
65+ yrs	(20)	29 (6-36)		(25)	13 (5-43)	
Smoking			0.23			0.09
No	(21)	36 (6-91)		(17)	>60 ^b	
Yes	(20)	>60 ^b		(28)	16 (5-32)	
Use of alcohol			0.27			0.003
None-moderate	(30)	91 (6-91)		(23)	>60 ^b	
Heavy	(5)	>60 ^b		(10)	12 (3-17)	
Grade			0.87			0.49
Well diff.	(24)	36 (6-36)		(19)	19 (5-22)	
Moderately diff.	(16)	>60 ^b		(21)	>60 ^b	
Poorly diff.	-			(3)	16 (16-17)	
Malignancy score			0.05			0.84
5-10	(20)	>60 ^b		(18)	43 (8-43)	
11-15	(17)	>60 ^b		(27)	17 (3-32)	
16-20	(3)	14 (14-16)		(2)	>60 ^b	
Angiogenesis			0.16			0.09
Under 8.5 vessels	(24)	31 (6-91)		(22)	17 (9-22)	
8.5+ vessels	(7)	>60 ^b		(10)	>60 ^b	
Inflammatory response			0.32			0.07
Light	(3)	>60 ^b		(7)	9 (8-14)	
Moderate or heavy	(40)	91 (6-91)		(43)	22 (3-43)	
Apoptosis			0.24			0.95
Under 1.4	(16)	91 (16-91)		(21)	17 (5-17)	
1.4+	(6)	17 (6-17)		(9)	22 (3-22)	
p53 expression			0.05			0.49
-	(16)	17 (6-29)		(21)	19 (9-32)	
+++	(21)	60 ^b		(25)	17 (3-43)	

^aP for the difference between early and late stage carcinomas was 0.01. ^bThe disease-specific survival rate was over 75%.

6 Discussion

6.1 Incidence

The incidence rate of cancer of the mobile tongue has remained low, the overall incidence being 0.6 per 100,000 person-years in Finland during the study period 1953-1994. This figure is slightly lower than those reported from Sweden (Östman *et al.* 1995) and Scotland (Macfarlane *et al.* 1992). In these studies, however, cancer of the base of the tongue was included in the figures. Cancers of the base of the tongue were excluded from the present study, as according to the International Union Against Cancer (1987), this cancer is categorised as a pharyngeal malignancy. The trend in incidence rates was, however, upwards in accordance with the earlier studies from developed western countries (Davis & Severson 1987, Macfarlane *et al.* 1992, Östman *et al.* 1995). An increase in incidence was seen in both men and women, which is also in agreement with the previous studies (Møller *et al.* 1989, Swango *et al.* 1996). The difference in incidence between the sexes was small, the rate being slightly higher among men throughout the study period.

In Northern Finland, the overall incidence rate of cancer of the mobile tongue was 1.0 per 100,000 person-years during 1974-1994. The figure was slightly higher than generally in the country. In a nationwide series there were as many as 803 (43%) patients for whom the sub-site of the cancer was unknown. One can speculate that there were cases with cancer of the base of the tongue included in this study population. Furthermore, the data set obtained from the Cancer Registry includes other cancers of the tongue besides SCCs. In Finland, 94% of the cancers of the tongue in men and 92% in women are SCCs (Dickman *et al.* 1999). Thus, the higher incidence of cancer of the mobile tongue in the northern part of Finland is even more pronounced. The nationwide incidence rate was standardised to the world population (Doll *et al.* 1966), whereas the incidence rate of Northern Finland was standardised to the population of the area as in 1984. The weights differ somewhat from each other, and any comparison of the incidence rates should hence be done with caution.

Similar to the nationwide data, there was a clear increase in incidence rates. Unexpectedly, the incidence rates were higher among women than among men

throughout the study period in Northern Finland. Furthermore, the incidence rate doubled in 21 years in women, whereas in men the increase was not so significant. In Iceland, in certain parts of Canada, in the Philippines and among the Maories of New Zealand, the age-standardised incidence rates of cancer of the tongue have been higher among women than men (Muir *et al.* 1987). In many other countries, including Sweden, the male-to-female ratio in cancer of the tongue has increased during the past 30 years (Östman *et al.* 1995). Age-standardised incidence rates for young patients under 40 years of age were not obtained in the present study, because the number of young patients remained very low throughout the study period.

Based on the present study, no clear explanation for the increase in incidence can be given. Smoking among the Finnish male population has been steadily decreasing since the late 1950s. Among women, the prevalence of smoking increased from the 1920s to the late 1970s, when it started to decrease. (Rimpelä 1978, Vierola 1996). One could presume that the increased percentage of smokers among females until the late 1970s would explain the increase in incidence rate in the 1980s and 1990s. However, only 30% of the female tongue cancer patients in Northern Finland were current or ex-smokers. In previous studies, the increased incidence of oral SCCs has been attributed to the consumption of alcohol (Møller 1989, Macfarlane *et al.* 1992). Indeed, the registered consumption of alcohol has increased in Finland from 2.0 litres of pure ethanol per person per year in 1955 to 7.1 litres in 1998 (Statistical Yearbook of Finland 1984 & 1999). In general, however, men tend to use more alcohol than women. In Northern Finland, only 18% of the present men and 2% of the women with cancer of the tongue were heavy drinkers. However, the increased consumption of alcohol might partly explain the increase in incidence of tongue cancer nationwide. The categorisation of the patients according to their tobacco and alcohol consumption was very rough in the present study. It is impossible to analyse retrospectively the exact amounts of tobacco and alcohol used by the patients. Nevertheless, as mentioned earlier, it has been concluded that smoking and heavy use of alcohol are not so obvious risk factors for cancer of the tongue as for cancer of the floor of the mouth (Franceschi *et al.* 1992, Jovanovic *et al.* 1993, Barasch *et al.* 1994). Thus, there must be other aetiological factors responsible for the increase in incidence rate seen among women in Northern Finland.

The use of snuff is rare in Northern Finland, and none of the patients were snuff users in the present study. If snuff were a remarkable risk factor for cancer of the tongue, one would expect high incidence rates in Sweden, where the use of snuff is common. The incidence rate, however, has remained rather low (1.2 per 100,000 person-years), even though it has increased in the past decades (Östman *et al.* 1995).

No other known aetiologic factors were investigated in the study. The dietary habits of the patients could not be recorded. Furthermore, the data on the patients' dental status prior to or at the time of the cancer diagnosis was available only in a few cases. The detection of *C. Albicans* or viruses is difficult in a retrospective work. None of the patients with cancer of the tongue in Northern Finland were HIV-positive or had had an organ transplant.

There were no major changes in patient characteristics over the study period. The sex distribution remained very much the same both nationwide and in Northern Finland. The patients' median age slightly increased over the 42-year period. In the area of Northern Finland, the patients' socio-economic status changed: in 1974-1980 all the patients had a

low socio-economic status as in 1988-1994 the proportion of patients with low socio-economic status was 84. This slight change was most probably due to improved educational status of the public in general over the years.

Despite the development of the health care system in Finland over the past 40 years, the stage distribution of cancers remained, unfortunately, very much the same throughout the study period both nationwide and in Northern Finland. This is in accordance with the previous studies (Silverman & Gorsky 1990, Mork & Glattre 1998). There was a slight decrease in the proportion of localised tumours seen in the last study period 1988-1994 nationwide. As the percentage of localised tumours decreased over the study period 1953-1994, the proportion of cases with unknown stage increased. Within the same period, the 5-year relative survival rate among the cases with unknown stage improved from 0% in 1953-1959 to 66% in 1988-1994. Thus, it seems that the group of unstaged tumours mainly consists of localised tumours. It might be that physicians aim to be as accurate as possible and leave the disease unstaged, if there is any doubt about the spreading of the tumour. Also, even if the TNM stage of the tumour is accurately recorded in the hospital files, it might be missing from the Cancer Registry files. In Northern Finland, the proportion of localised diseases (TNM stages I-II) increased from 31% in 1974-1980 to 52% in 1988-1994.

The proportion of localised tumours in the nationwide data was almost the same as that reported from Norway. There was, however, a difference in the distribution of regional and distant diseases between the two countries. In Finland, 18% of the cases were regionally and 10% distantly spread at the time of diagnosis, whereas the corresponding figures in Norway were 37% and 2%. It seems that the staging systems differ between the cancer registries of Finland and Norway. In the present study distant disease was described as "cancer spreading beyond the tongue or having involved the tissues beyond those immediately draining the tongue", whereas in the Norwegian survey the disease was considered distant if the cancer had spread beyond the regional lymph nodes. Thus, it is very probable that there are cases with regional disease in the Norwegian study population which would have been classified as distant according to the staging system of the Finnish Cancer Registry. (Mork & Glattre 1998). In a study by Silverman & Gorsky (1990) on a population-based SEER (Surveillance, Epidemiology, and End Results Program) series in the United States, the tumours were staged simply as localised and spread. They found that 52% of the patients with cancer of the mobile tongue had a spread disease at the time of diagnosis. The lower frequency of spread cases reported in the present series and in the Norwegian study is probably due to the well-functioning health care systems in the Scandinavian countries. Both in Finland and Norway, health care is based on a national health insurance scheme, which allows equal access to medical and hospital services for everyone (Hakulinen *et al.* 1986). It might be that there are tongue cancer patients in the United States who postpone seeking medical advice for economical reasons.

Instead of the generally used 5-year periods, the incidence rates were here analysed in 7-year periods. This was due to the small number of patients in Northern Finland. Since the incidence rates were calculated from a population-based series, the internal validity of the study is good. However, as the disease is fairly rare, substantial random errors may occur, especially in the data of Northern Finland. Nevertheless, the external validity of the

study is good, and the results are comparable to the population-based incidence studies conducted in other western industrialised countries.

6.2 Detection

According to the present study, the diagnostic skills of the physician/dentist first contacted by the patient had a significant effect on the patient's prognosis. If cancer was not detected at the initial visit and no follow-up visit was scheduled, the delay in diagnosis was often fatally long. The results of the present study confirm the findings made by others that the length of professional delay is a significant prognostic factor (Allison *et al.* 1998a).

The length of patient delay was not related to the disease-specific survival time. This is in accordance with the reports by Kowalski *et al.* (1994) and Wildt *et al.* (1995). Interestingly, patient delay was very short, only 0.6 months, in the misdiagnosed cases left without follow-up. It is probable that these tumours were at an early stage when the patients first sought medical advice. Thus, it was particularly unfortunate to notice that these cases were misdiagnosed and the patients were left with a false sense of security.

The most important factor influencing the referral pattern was the patient's primary symptom at the initial appointment. The more closely the primary symptom was related to the tongue, the more often the patient was correctly referred. If the reason for the medical appointment was totally unrelated to the oral symptoms, the patient was most likely to be left without a scheduled follow-up. Even though all patients mentioned their oral symptoms during the initial medical visit, it seems that both physicians and dentists focused on the matter the appointment had been made for. Thus, the inspection of the mouth may have remained superficial in these cases. Similarly, Allison *et al.* (1998b) found that the patients with comorbidity present at the initial appointment carried a risk for delayed referral. Referring to the findings of the present study, it is easy to agree with Allison *et al.* (1998b) that physicians/dentists tend to neglect the innocuous symptoms of early stage carcinoma and rather focus on the disease they are formerly aware of.

Opposite to the Canadian (Allison *et al.* 1998b) and Danish (Wildt *et al.* 1995) studies, the patient's age did not have an effect on the professional delay in the present study. It was, however, unfortunate to find that the patients incapable of living independently at home and with a low socio-economic status had a significant risk for delayed referral. It might be that patients with higher educational status are able to describe their symptoms in a more specific manner than patients with a lower educational status.

Only 14 (19%) of the 75 patients first consulted a dentist in the present study. The figure is much lower than those reported in Denmark and England (Scully *et al.* 1986, Wildt *et al.* 1995). This is probably due to the cultural differences between the areas. The number of dentists was small in Northern Finland until the 1970s, and it was the physician who also treated many dental problems in rural areas. Thus, as the majority of the patients in the present study were elderly, they were used to visiting a physician even in the case of oral symptoms. Furthermore, they were probably not aware of the ability of dentists to diagnose oral diseases other than those directly related to teeth.

In the present study, the primary care files were obtained in 87 out of 105 cases. There were ten patients who developed a carcinoma during a hospital follow-up and two cases diagnosed incidentally in the referral centre. This leaves 18 (17%) cases with missing data, which is a considerable number. In the missing cases the primary care files either had been destroyed due to the death of the patient or were simply not found or sent. However, when the 18 cases with missing data were compared to the 75 cases, no significant differences in any of the studied demographic or tumour-related factors except in sex distribution were observed between the groups (data not shown). Thus, the results of the present study can be generalised to a population-based sample, and the internal validity can be considered good. The results of the present study, however, cannot be directly applied to the studies conducted in countries, where health care is not provided by the state.

As the stage distribution of cancer of the tongue has remained approximately the same in the past 40 years in Finland, more efforts should be made towards shortening the delay in diagnosis. According to the literature, the length of patient delay has remained the same over the decades in Europe and the United States (Hackett *et al.* 1973, Wildt *et al.* 1995). It thus seems that the growing public knowledge of oral cancer detection has had a small effect on patient delay. As mentioned earlier, there is a group of patients who deliberately deny or ignore their symptoms or signs. Such behaviour is likely to be due to a fear of cancer and public campaigns have thus not had the effect hoped for.

Furthermore, there are problems in determining the patient delay. The previous studies on patient delay have been done either by interviewing the patients or by asking them to fill in a questionnaire (Guggenheimer *et al.* 1989, Wildt *et al.* 1995). The data have been collected right after the cancer diagnosis, when the patients are usually emotionally upset and desperate to find an explanation for the onset of their cancer. It is therefore very unlikely that the patients are able to name the exact date when the symptoms first occurred. Furthermore, it is impossible to determine when the tumour has become clinically visible. Therefore, the data on patient delay are inaccurate and frequently biased.

Professional delay is an accurate measure and has proved to have a significant effect on the prognosis of the patient. Thus, strategies to reduce professional delay should be encouraged. This could be achieved by further education of primary care physicians and dentists. The physicians'/dentists' skills to perform a thorough oral examination, including palpation, and biopsy should be improved. However, according to the present study, the detection rate of cancer of the tongue was one per 375,700 visits in a Finnish primary health care practice. This means that an average medical general practitioner in Northern Finland might not see a single case of cancer of the tongue during his/her career. The odds would be even smaller for a dental practitioner, as only 19% of the patients first consulted a dentist. In this respect, the median professional delay noted in the present study was very acceptable, only 0.7 months.

As mentioned earlier, the effectiveness of screening for oral cancers has been proved recently in India (Sankaranarayanan *et al.* 2000). In the European countries, the value of screening programs has not been proved (for a review, see Rodrigues *et al.* 1998). The incidence rate of oral cancer is many times higher in India than in Finland and thus, based on the current knowledge, it seems that there is no reason to recommend a population-based screening program for oral cancer in Finland. However, as a thorough examination

of the oral cavity is part of a routine dental check-up, public should be encouraged to visit a dentist on a regular basis. This could be achieved by including all age groups under dental care reimbursed by the health insurance. At least the dental care of the elderly should be included in the general insurance scheme. Furthermore, regular oral examinations of the elderly persons living in institutions should be arranged by the communities.

6.3 Survival

Even though the incidence of tongue cancer increased and the stage distribution of the disease remained the same over the study period, the overall 5-year relative survival rate improved from 40% in 1953-1959 to 58% in 1988-1994. The most important factor influencing survival rate was the stage of the tumour at the time of the diagnosis, which was accordant with the study by Dickman *et al.* (1999). The improvement in the 5-year relative survival rate in the present study was seen in localised and especially regional disease, whereas in distant disease the survival rate remained low throughout the study period.

Some improvement in the 5-year relative survival rate was seen in both sexes. The figures were slightly better among women, which can be explained by the larger proportion of localised tumours in women. In a previous Finnish study, however, the 5-year relative survival rate of cancer of the tongue was reported to be lower in men than in women even within the group diagnosed for localised disease (Dickman *et al.* 1999). Overall, the 5-year relative survival rates in the present study were higher than those in the study by Dickman *et al.* (1998). In this work, however, all cancers of the tongue were included in the study, whereas in the present study only cancers of the mobile tongue were included. As concluded by Berrino *et al.* (1998), cancers at the tip, at the lateral side or on the ventral surface of the tongue have significantly better survival rates than those arising on other sub-sites. In the present study, in 1953-1959 the sub-site of the cancer was specified in very few of the cases, whereas in 1988-1994 the sub-site was unknown in only one fifth of the cases. It might be that the 5-year relative survival rate of cancer of the mobile tongue has not increased as much in reality as described here. There has probably been a larger proportion of cancers of the base of the tongue at the beginning of the study period compared to the end of it, which might be reflected in the survival.

The relative survival rates improved in both age groups, especially among the older patients aged 65 years or over. There were only minor differences in the survival rates between the two age groups in 1981-1987 and 1988-1994. According to Dickman *et al.* (1999), however, the oldest patients with cancer of the tongue (aged over 75 years) had the lowest relative survival rates.

The figures of the present study are in accordance with the Norwegian study where a national cancer registry material was analysed. In the study, the 5-year relative survival improved both in men and in women during 1953-1992, even though the stage distribution of the disease remained the same. The Norwegian study included all oral cancers. Nevertheless, cancer of the tongue accounted for 43% of all the oral cavity cancers in the study. (Mork & Glatre 1998). The results are further in accordance with a

study by Franceschi *et al.* (1993), in which a significant improvement in both early and late stage cases of cancer of the tongue was observed between the years 1967-1977 and 1978-1987. In this particular study, too, the stage distribution of the tumours remained the same over the study period. Thus, one can easily agree with Franceschi *et al.* (1993) that it is the improved treatment of cancer that is reflected in the survival rates. However, it was clearly seen in the present study and in the study by Mork & Glattre (1998) that the 5-year relative survival rate remained low among the cases with distant disease. Thus, further efforts should be made to aim at early diagnosis of cancer of the tongue.

The 5-year relative survival rates observed in both the present study and the study by Dickman *et al.* (1999) are higher compared to the rates generally reported in Europe (Berrino *et al.* 1998). It has been observed that in the countries where cancer treatment is centralised, as in Finland, the survival rates are better compared to those where it is not (Berrino *et al.* 1998).

Moreover, as the study was done on a large population-based material, the internal validity of the results can be considered good. Furthermore, the survival figures can be compared to the figures obtained from other western industrialised countries, where the treatment schemes of cancer are somewhat similar to that in Finland.

6.4 Prognostic factors

The prognostic importance of the TNM stage of the tumour was once again proved in the present study. Moreover, local spread of the tumour had a more profound effect on the prognosis than the presence or absence of positive neck nodes at the time of diagnosis. It turned out that the majority of the known demographic and histopathological prognostic factors were related to the stage of the tumour. Thus, a stratified analysis was used to detect the most relevant demographic and histopathological prognostic factors in early and late stage tumours separately. According to the present study, older age of the patient, a high malignancy score of the tumour and the absence of p53 staining detected in IHC predicted a poor prognosis in early stage carcinomas.

There are only a few previous studies in which several prognostic factors have been studied in a homogeneous patient group. Högmo *et al.* (1999) found that Jakobsson's malignancy grading system and overexpression of p53 predicted regional recurrence in small stage I tongue carcinomas. Leedy *et al.* (1994) concluded that only the depth of the tumour had a prognostic value in stage T1-2 tongue carcinomas. In that study, no correlation between tumour angiogenesis or p53 expression and the presence of metastatic neck nodes was found. In a study by Gluckman *et al.* (1997), none of the factors studied (grade, Bryne's malignancy score, tumour angiogenesis and p53 expression) predicted tumour behaviour in small T1 carcinomas of the tongue and the floor of the mouth. Nevertheless, a high Bryne's malignancy score tended to be related to an aggressive nature of the tumour (Gluckman *et al.* 1997). Furthermore, in a French study on patients with head and neck carcinomas, older age of the patient (over 60 years) and positive neck node status at the time of diagnosis were significantly related to poor overall survival. None of the histopathological factors analysed in that study (tumour angiogenesis, mitotic index, grade, nuclear grade, keratinisation, desmoplasia, growth

pattern, inflammation, tumour emboli in peripheral vessels, keratin 6, 13, and 19 expression, cytofluorometric ploidy and S-phase) had any prognostic value. (Janot *et al.* 1996).

In the present study, the old patients aged over 65 years with an early stage tongue carcinoma had a poorer prognosis than the younger ones. Moreover, when the study material was not stratified by stage, the patients aged 44 years and less had a better prognosis than the older ones. The result is in accordance with the study by Dickman *et al.* (1999), in which poor relative survival rate was observed among old (aged 75+ years) patients. Friedlander *et al.* (1998) compared the disease-specific survival times by tumour stage between younger (under 40 years of age) and older patients with cancer of the tongue, but found no difference. They did note, however, that the locoregional failure rate was higher among the younger patients, although the difference was not statistically significant (Friedlander *et al.* 1998). In the present study, the mean recurrence-free times were longer among the patients aged under 45 years especially among the late stage cases. In the late stage cases, the mean recurrence free time was 122 (95% CI 58-186 months) among patients aged under 45 years and 69 months (95% CI 35-104 months) among those aged over 65 years.

Furthermore, Mork & Glatre (1998) found that the relative survival rates of young oral cancer patients (aged under 35 years) were significantly better than those of the older age groups. The better rates were seen even when the cases were stratified by tumour stage. Moreover, Janot *et al.* (1996) found that head and neck SCC patients aged less than 60 years had a better prognosis than the older patients. In conclusion, there are contradictory data on the prognostic value of the patient's age. However, the present study and more recent literature have shown that old age is related to a poor prognosis.

A high Bryne's malignancy score correlated significantly with poor survival in early stage carcinomas. The result is in a agreement with Gluckman *et al.* (1997), who noted that a high malignancy score was related to tumour aggressiveness in patients with small tongue carcinomas, even though the relationship was not statistically significant. According to Högmö *et al.* (1999), Bryne's malignancy score did not have a prognostic value in small, stage I tongue carcinomas. In that particular study, however, the malignancy score was analysed in four subgroups (degree of keratinisation, nuclear polymorphism, pattern of invasion and lymphoplasmacytic infiltration). Thus, the results of Högmö *et al.* (1999) and the present results cannot be directly compared. Unexpectedly, Högmö *et al.* (1999) found that Jakobsson's malignancy grade did predict tumour recurrence, as Bryne's malignancy scoring is based on the method introduced by Jakobsson *et al.* (1973). According to Bryne *et al.* (1989), malignancy scoring should be done on the deepest invasive part of the tumour. In the present study, the different histopathological prognostic factors were determined from the pre-treatment biopsy sections. The deepest invasive part of the tumour was present in only 26 (29%) of the samples. Thus, the malignancy score was determined from the most lateral part of the tumour present in the sample. One could speculate that the prognostic value of the score would have been even more pronounced if there had been a possibility to analyse the most invasive parts of the tumours.

The present study revealed that the absence of p53 staining detected by IHC was related to a poorer prognosis in early stage cancers of the tongue. Again, the result was opposite to the study by Högmö *et al.* (1999), who found that overexpression of p53

predicted regional recurrence in small tongue carcinomas. However, there are several earlier studies in which no correlation has been seen between the expression of p53 in IHC and the prognosis of patients with cancer of the tongue or oral cavity (Leedy *et al.* 1994, Gluckman *et al.* 1997). Thus, it seems that the role of p53 in predicting prognosis of cancer of the tongue still remains somewhat unclear.

As mentioned earlier, p53 mutations may permit tumour growth in hypoxic areas (Graeber *et al.* 1996). Maeda *et al.* (1998) found elevated VEGF levels in the most necrotic areas of the tumour, which may indicate that hypoxia induced VEGF expression. Furthermore, they found a trend towards a positive correlation between VEGF and the mutated p53, though the trend was not statistically significant. Thus, it seems that the mutated p53 might have a role in tumour neovascularisation. However, no relationship between tumour angiogenesis and the expression of p53 was found in the present study.

According to the present study, a low apoptotic index tended to be associated with a better prognosis in the early stage cases. However, the trend was not statistically significant. This was probably due to the small number of cases with a high apoptotic index (only six) and the large proportion of censored cases in the analysis. Apoptosis is complementary to mitosis in regulating cell populations in both physiological and pathological conditions (Kerr *et al.* 1972). Jäckel *et al.* (1999) noted that the number of apoptotic cells correlated with mitotic activity and tumour spread at the time of diagnosis in laryngeal carcinomas. They hence concluded that a high frequency of spontaneous apoptosis reflects a more rapid growth rate of the tumour. The results of the present study seem to reinforce these findings (Jäckel *et al.* 1999). Nevertheless, the results are opposite to those obtained by Xie *et al.* (1999), who found a low apoptotic index in cancers of the tongue to be related to a poor prognosis. Xie *et al.* (1999) further noted that a combination of proliferative and apoptotic parameters was an even more powerful prognostic factor than the apoptotic index itself. In the present study, the proliferation factors were not studied. Apoptosis has not been studied much in oral SCCs, and more research in larger patient series is needed to evaluate its prognostic value. It seems that the apoptotic index should be investigated instead of the regulator proteins of apoptosis, as it has been observed that the expression of the proteins and the rate of apoptosis are not related to one another (Jäckel *et al.* 1999). Furthermore, a combination of proliferation factors and the apoptotic index might be useful in future research.

There was a trend showing that heavy angiogenesis of the tumour was associated with a better prognosis in both early and late stage cases. Neovascularisation of the tumour cannot be determined with the techniques currently in clinical use. Thus, tumour angiogenesis does not necessarily reflect neovascularisation at all. Furthermore, due to the high vascularity of the oral cavity, tumours of this region may be less dependent on neovascularisation. (Gleich *et al.* 1997). In previous studies, the microvessel counts have been mostly performed from the “hot spot“ area of the section, i.e., the part of the section with the highest microvessel density. In view of the facts mentioned above, the “hot spot“ area probably does not reflect abundant neovascularisation in the area. Nevertheless, the technique used in the present study, where the mean numbers of microvessels in ten randomised high-power fields within the tumour were calculated, is not any better in this respect. Since the detection of microvessels does not necessarily provide any information about tumour neovascularisation, the role of the vascular endothelial growth factor (VEGF) should be further studied.

The inflammatory infiltrate at the periphery of the tumour had no prognostic value in early stage tumours. In late stage tumours, however, there was a tendency towards a better prognosis among the patients with high or moderate inflammatory infiltrate at the margin of the tumour. It may be that the role of inflammatory infiltrate is more pronounced in late stage tumours. Of the present early stage tumours, 34% had heavy inflammatory infiltrate at the periphery of the tumour, while the corresponding figure for the late stage tumours was 46%. This could be taken to indicate that the possible host response occurs at a more advanced stage of the disease, and, furthermore, that the intensity of the response is reflected in the prognosis of the patient. Nevertheless, as stated before, the role of the immune system in carcinogenesis is still largely unknown.

Human papilloma virus (HPV) was not detected in a single case in the present study. Two sensitive methods, *in situ* hybridisation and the PCR method were used to detect the virus. PCR with β -actin primers gave a positive result in every sample. This does not, however, exclude the possibility that the virus has been present but has then disappeared (“hit and run“ mechanism). Nevertheless, according to the present study and the earlier studies (Chiba *et al.* 1996, Rietdorf *et al.* 1997, Pintos *et al.* 1999), HPV cannot be considered a prognostic factor of oral SCC.

Only a limited number of the histopathological prognostic factors proposed in the literature were evaluated in the present thesis. The factors analysed in the present study were chosen according to the principle that those clinically easiest to detect and those known to correlate with one another were included. Since the tissue material from pre-treatment biopsies is limited, it might be useful to analyse certain promising prognostic factors in postoperative preparation blocks to confirm their reliability.

7 Summary and conclusions

The incidence of cancer of the tongue has increased both in Europe and in the United States over the past decades. The increase in incidence has been obvious among young men. Tobacco smoking and increasing consumption of alcohol have been blamed for the trend seen in the incidence. Cancers of the tongue are even today diagnosed at a rather late stage. The delay in seeking medical advice after the onset of cancer symptoms has remained the same over the past few decades. This is unfortunate, as the TNM stage of the tumour is strongly associated with patient survival. There has not been any improvement in survival rates among the patients with distant spread cancer of the tongue. Even though the TNM stage of the tumour is the most important prognostic factor of cancer of the tongue, there is a sub-group of localised stage I cancers which behave in an unexpectedly aggressive manner. No indisputable prognostic factors have been found to predict aggressiveness of localised cancers of the tongue.

To analyse the trends in the incidence and survival of cancer of the mobile tongue in Finland, the data provided by Finnish Cancer Registry were used. A total of 1504 new cases with cancer of the mobile tongue emerged during 1953-1994 in Finland. To evaluate patient and tumour characteristics, early detection and various prognostic factors of tongue cancer, all the patients diagnosed to have cancer of the mobile tongue in a geographically defined area of Northern Finland in 1974-1994 were identified. A total of 105 new cases with cancer of the mobile tongue emerged during the study period. The patients' hospital files were reviewed to gather data on patient and tumour characteristics. Furthermore, the source of referral was obtained from the hospital files. To evaluate the early detection of cancer of the tongue, the patients' primary care files were retrieved. Finally, to analyse various prognostic factors of cancer of the tongue, the patients' hospital files were once more reviewed for demographic and clinical prognostic factors. The histopathological prognostic factors were analysed from the patients' pre-treatment biopsies.

Among men, the incidence rate of cancer of the mobile tongue decreased from 0.9 per 100,000 person-years in 1953-1959 to 0.5 per 100,000 person-years in 1967-1973, after which it steadily increased to 0.8 in 1988-1994. Among women, the incidence rate of cancer of the mobile tongue decreased from 0.56 per 100,000 person-years in 1960-1966 to 0.4 per 100,000 person-years in 1981-1987, but then increased to 0.6 per 100,000

person-years in 1988-1994. In Northern Finland, the incidence rate doubled in women from 0.7 per 100,000 person-years in 1974-1980 to 1.4 per 100,000 person-years in 1988-1994, while among men the incidence rates were 0.6 and 1.0 per 100,000 person-years respectively. No clear explanation for the increase was observed. However, the increased consumption of alcohol might explain at least part of the trend seen in a nationwide data set. The proportion of localised tumours decreased over the 40-year study period, while the proportion of cases with unknown tumour stage increased. There were no significant changes in the patient and tumour characteristics during the 20-year study period.

The patients who remained undiagnosed and were not scheduled for a follow-up visit after the initial visit in primary care had a significantly poorer prognosis compared to those referred immediately. The better the patient was able to identify his/her symptoms in the tongue, the more likely he/she was to be referred immediately to the referral centre. This indicates that physicians/dentists focus on the symptom the appointment is made for and do not necessarily perform a thorough oral examination, which may lead to a misdiagnosis. Moreover, it was unfortunate to find that the patients incapable of living independently at home and with a low socio-economic status had a significant risk to be misdiagnosed at the initial visit.

The relative survival rates have improved in both sexes and in both age groups and in the cases with both localised and regionally spread tumours during the past decades. Among the cases with distant spread tumours at the time of diagnosis, the 5-year relative survival rates remained low. Since the stage distribution of tumours has remained the same throughout the decades, the increase in survival rates is most probably due to the improvements in cancer treatment.

According to the present study, the patient's old age, a high malignancy score and an absence of p53 in IHC staining predicted a poorer prognosis in the cases with early stage (TNM stage I-II) cancers of the tongue. Nevertheless, the results of the present study should be interpreted with caution, as the patient material was rather small and the quality of the pre-treatment biopsy sections varied greatly.

As a conclusion, the incidence rate of cancer of the mobile tongue has increased in both sexes over the past two decades in Finland. Unexpectedly, in Northern Finland, the incidence rate of cancer of the mobile tongue was higher among women than among men throughout the 20-year study period. No changes in patient and tumour characteristics were observed during the study period.

The diagnostic skills of the medical professional first contacted by the tongue cancer patient had a profound effect on the patient's prognosis. As the relative survival rate of distant spread cancers of the mobile tongue remained low during the whole 40-year study period, efforts should be made to recognise tongue cancers as early as possible. Regular dental check-ups should be encouraged, as dentists have a good opportunity to recognise symptomless, early stage cancers of the tongue. Furthermore, a thorough oral examination, including palpation, should be performed on every patient who complains of oral symptoms, even incidentally.

In the present study, an old age of the patient, a high malignancy score and an absence of p53 in IHC staining predicted a poorer prognosis in small localised cancers of the mobile tongue. The early stage cancers with these qualities should be evaluated and possibly treated in a more aggressive manner.

8 References

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