Oral squamous cell carcinoma; some epidemiological and clinicopathological aspects

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VRIJE UNIVERSITEIT

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You can study cancer for years but you only learn it’s true nature when one of your loved ones is stolen by it

Pap, je hebt in de jaren vele stellingen voor me bedacht die ik alle genadeloos afkeurde, wat zou ik graag nog wat van die stellingen van je horen!

Contents

Chapter 1

Introduction and aim of the study

Introduction

Head and Neck cancer is the 7th most common cancer worldwide. For oral cancer alone, in the year 2000, 266.672 new cases occurred worldwide (1). Oral cancer represents approximately 2 percent of all new cancer cases worldwide (2). Oral cancer occurs more often in men than in women. The worldwide male female ratio nowadays is approximately 1.5:1 (3). More than 90% of oral cancers consist of squamous cell carcinoma.

In the majority of patients, oral cancer occurs in the 5th through 8th decade of life. The mean age of the patients in a survey of the US population in the period 2000-2004 was 62 years (4). In the literature there are indications of an increasing number of patients below 40 years of age. This increase started in the mid seventies, persisted until the late eighties and then remained stable (5, 6).

The most important etiological factors are tobacco and alcohol use. Human papillomavirus (HPV), particularly type 16, seems to play a role in a small subset of patients with oral cancer (7).

Oral cancer can present itself as an indurated ulcer or as a red, white or combined patch; some tumors show exophytic or verrucous growth (1). Tumors may arise in any part of the oral cavity, but the tongue and the floor of mouth are the most common sites (6,8). In an actually unknown percentage of cases, oral cancer is preceded for months or even years by clinically visible precursor lesions, in particular leukoplakia and erythroplakia.

Treatment of small (T1 or T2) oral squamous cell carcinoma consists in general of surgery, if necessary combined with radiotherapy in case of lymph node metastasis, extranodal spread or incomplete resection of the primary. In advanced tumors (T3,T4), apart from surgery, chemoradiation may be the treatment of choice.

In Europe, the oral cancer mortality rate has been declining over the last decade; a few countries i.e. Poland, Bulgaria, Belarus and Romenia still have increasing mortality rates in men (9). The survival rate decreases in patients with lymph node metastases and distant metastases. The overall survival rate for all stages together (regardless of different sizes and absence or presence of lymph node and distant metastases) is approximately 50%-55%, the survival rate for stage I and II is 70-85%. The worldwide estimated number of patients who died from oral cancer was 127.000 in 2008 (2).

Aim of study

The present study is mainly focussed on the clinical relevance of a number of histopathological aspects of small (T1, T2) squamous cell carcinomas (SCC) of the tongue and floor of mouth. In addition, some epidemiological aspects have been studied.

In chapter 3 the clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma is described; in chapter 4 the status of the deep surgical margins in tongue and floor of mouth carcinoma is studied in relation to local recurrence. All patients registered in the registration system of the VU University Medical Center (formerly known as Free University Medical Center) between 1985 and 1995 were included in these studies.

In chapter 5 two different histopathological grading systems are compared in relation to a number of clinical parameters and outcome. The classical Broders' grading has been compared with the more recently advocated malignancy grading system. This study was performed in 128 patients with previously untreated T1 and T2 SCC of the tongue and floor of the mouth.

In chapter 6 possible differences in survival between patients with oral cancer developing from pre-excisting oral leukoplakia and patients with de novo oral cancer have been studied.

Chapter 7 is dealing with oral cancer in The Netherlands. Two groups of oral cancer patients from different periods of time (1980-1984 versus 2000-2004) are compared with regard to male-female ratio, age of the patients, site, TNM-stage and smoking and alcohol use.

References

1. Barnes L, Eveson JW, Reichart P, Sidransky D. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours. IARC Press: Lyon 2005 ISBN 92 832 2417 5

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.

3. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009; 45: 309-316.

4. Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER web site, 2007.

5. Llewellyn CD, Johnson NW, Warnakulasuriya KAAS. Risk factors for squamous cell carcinoma of the oral cavity in young people; a comprehensive literature review. Oral Oncol 2001; 31: 401-418.

6. Muller S, Pan Y, Li R, Chi A. Changing trends in oral squamous cell carcinoma with particular reference to young patients: 1971-2006. The Emory University experience. Head and Neck Pathol 2008; 2: 60-66.

7. Leemans C, Braakhuis BJM, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011; 11: 9-22.

8. Moore SR, Johnson NW, Pierce AM, Wilson DF. The epidemiology of tongue cancer: a view of global incidence. Oral Dis 2000; 6: 75–84.

9. Bonifazi M, Malvezzi M, Bertuccio P, Edefonti V, Garavello W, Levi F, La Vecchia C, Negri E. Age-period-cohort analysis of oral cancer mortality in Europe: The end of an epidemic? Oral Oncol 2011; 47: 400-407.

Chapter 2

Oral cancer; some aspects of the etiology, diagnosis, histopathology and staging

Etiology

The most important etiological factors are tobacco and alcohol. Especially when combined, the risk of oral cancer increases significantly (1,2). There is a strong dose response relationship, and both alcohol and tobacco can induce oral cancer by itself. However, most cases result from the combined effect of smoking and drinking. The exact mechanism of the carcinogenic effect of alcohol remains unclear. It has been suggested that alcohol causes a greater permeability of the mucosa which thereby facilitates the penetration of carcinogenic agents from tobacco products. Alcohol is considered to affect also the intracellular transport mechanisms but further studies are necessary to investigate the exact pathways (3,4).
Since the 1980's there is a decrease in the number of smokers. The incidence rates of head and neck squamous cell carcinoma has roughly paralleled trends in smoking. However, incidence rates of oral and oropharyngeal cancer are increasing (5). This pleads for the presence of other etiologic factors, such as human papillomavirus (HPV) infection. The last decade a lot of research was done, indeed, in the field of HPV related cancers. It was already known that HPV plays a role in the occurrence of cervical cancer. At present, HPV exposure and infection have particularly been associated with the risk of oropharyngeal cancers.
The HPV virus, especially the HPV type-16, leads to E6 and E7 activity. Expression of these oncogenes leads to inactivation of p53 and RB, leading to serious disturbances of the cell cycle regulation (6,7). Current opinion is that head and neck squamous cell carcinomas (HNSCCs) have different molecular subgroups, being HPV-positive and HPV-negative tumors. Tumor HPV status is considered to be an independent prognostic factor. HPV positive tumors are associated with better survival and lower risk of local recurrences and second primary tumors (8). HPV- negative tumors are more frequently associated with smoking and alcohol. For oral cancers, the influence of HPV infection is still under debate, although a recent meta-analysis showed a strong association between the presence of HPV DNA and oral squamous cell carcinoma, especially for HPV16 (9).
The possible role of dental prosthesis in alveolar ridge carcinoma has been studied in the past. Denture use was not an independent risk factor for OSCC (10). Another etiological factor which plays an important role in South Asia is betel nut chewing. Because of this different etiological factor, the site distribution (buccal cancer being the most commonly affected subsite) and male-female ratio is rather different from those in Western

Countries (11,12).
Other etiological factors that are mentioned in the literature - but without consensus about their role - are immunosuppressive therapy, poor oral hygiene, and protective role of diet (frequent consumption of vegetables and fruit).

Diagnosis

Because the prognosis of the patient decreases with increasing tumor stage it is of great importance to detect the tumor as early as possible. This early detection is compromised by multiple factors varying from tumor behaviour to patients' and doctors' delay.
Several authors have studied the effect of screening programs. Although the mouth is easy to access and to examine, regular screening programs for oral cancer are complicated by several factors. There is no consensus concerning the screening interval. Another factor is the cost-effectiveness of regular screening programs. In developed countries oral cancer is not a common disease. However, it might be beneficial to screen high risk patients (patients who abuse alcohol and tobacco) although these patients are often subject to non-compliance (13,14).
Instead of regular screening it might be more effective to concentrate on prevention like cessation of alcohol and tobacco habits (14). Alcohol as risk factor for oral cancer is not commonly recognized by dentists and general practitioners, necessitating awareness among the medical professionals (4). The study of Macpherson et al. (15) pleaded for continuing education programs for dental as well as medical care professionals including diagnostic skills and prevention.
Diagnosis of OSCC is confirmed with a biopsy for histopathological examination. This is still the gold standard. Some clinicians use toluidine blue vital staining as a diagnostic aid. It may help the clinician to differentiate areas of epithelial dysplasia, CIS (carcinoma in situ) or invasive carcinoma from normal tissue. Toluidine blue is a metachromic dye, used as nuclear stain binding to DNA (16). Dysplastic and malignant tissues may retain toluidine blue due to loss of tumor suppressor genes (17). Onofre et al. (18) found a sensitivity of 77% and a specificity of 67%. There were no false negative results in the detection of CIS and invasive carcinoma. However, toluidine blue is less sensitive for premalignant lesions with false negative rates up to 58%. In conclusion, toluidine blue can be a helpful tool but should not replace a biopsy.

Promising studies have been performed in the field of salivary biomarkers. In saliva of patients with an oral squamous cell carcinoma altered expression of proteins and mRNA markers are observed. A panel of different protein and mRNA markers has been studied that could discriminate between OSCC patients and control samples. Further studies are required to obtain a convenient salivary test which is easy to use, with high sensitivity and specificity (19). Other clinical non invasive diagnostic aids are light based screening aids (ViziLite, VELscope), autofluorescence and brush biopsy. None of these tools are as reliable as histopathology.

Imaging

Nowadays, Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) are often used as additional diagnostic tools apart from conventional x-ray imaging like orthopantomography. The CT scan gives better information on the possible invasion of bone, whereas the MRI gives more information on the extent of the tumor and possible nodal involvement (WHO).

A recent review showed the importance of positron emission tomography (PET). PET/CT can be useful for the staging of oral squamous cell carcinoma as well as the follow-up of OSCC patients for its high accuracy to detect distant metastases and second primary cancers (20). This is particularly of interest for patients with an advanced stage of the disease where the risk of distant metastases is increased (21).

Histopathological aspects

Oral squamous cell carcinoma is a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and the prescence of intercellular bridges (22). Histopathologic grading is widely used to indicate the tumor aggressiveness. This grading is based on the system of Broders (22), modified by the WHO (23). This grading specifically studies the degree of keratinisation, nuclear polymorphism and mitotic activity (grade I-III; well differentiated, moderately differentiated, poorly differentiated). In the last three decades modifications of this grading system have been developed. Most widely used is the Malignancy Grading System of Anneroth and Bryne (24,25). The latter advised to perform the grading at the tumor front because the cells at the tumor front are different from the cells in more superficial parts of the tumor.

This was supported by the study of Sawair et al. (26). The mean invasive front grading scores were strongly associated with overall survival.

Histopathological findings with prognostic value are state of the surgical margins, pattern of invasion, tumor differentiation, T-stage, perineural invasion, vascular invasion, positive lymph nodes and extracapsular spread of metastatic lymph nodes (27).

The status of the resection margin has prognostic value. In the literature different definitions are given for tumor free margins. A clear margin is defined as "no tumor within 5 mm distance of the margin", close margin as "tumor within 5 mm distance of the margin", and positive margin as "tumor cells in the margin" (28,29). There is no consensus about the relevance of the presence of dysplasia or carcinoma in situ in the margin or close to the margin. However, there are strong indications that dysplasia in the surgical margin is a predictor of local recurrence (30,31).

Close margins may be associated with indicators of aggressive tumor behaviour like perineural spread and unfavourable pattern of invasion. Slootweg et al. (32) found a significantly higher number of distant metastases and local recurrence in patients with non tumor free margins. This was not in accordance with the findings of Brandwein-Gensler et al. (33). They found that margin status alone was not an independent factor for the prediction of local recurrence. However, in that study the presence of dysplasia or carcinoma in situ was not mentioned.

In recent years, a number of studies have been reported in which molecular markers have been used to assess the status of the surgical margins in relation to local recurrence (34).

Staging

Malignant tumors of the body are usually classified with the TNM-classification. This system is also used worldwide for tumors of the oral cavity. The system was developed by the Union for International Cancer Control (UICC). It is a widely used system to indicate tumor size (T), metatases to the lymph nodes in the neck (N) and distant metastases (M). The most recent edition of the TNM-classification and the staging system is depicted in table 3 (1).

ICD-codes, international classification of diseases (WHO), are the international standard for the registration of general epidemiological studies, health related studies, and clinical use. Malignant neoplasms of

the lip and oral cavity are separately indicated (C00-C14). Every specific site has its own ICD-code. For example, a malignant tumor at the border of the tongue is indicated as C02.1.
World wide, approximately 50% of patients with oral and oropharyngeal cancers present at first admission with stages III and IV (35).

References

1. Gupta PC, Murti PR, Bhonsle RB. Epidemiology of cancer by tobacco products and the significance of TSNA. Crit Rev Toxicol 1996; 26: 183-198.
2. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988; 48: 3282-3287.
3. Wight AJ, Ogden GR. Possible mechanisms by which alcohol may influence the development of oral cancer - a review. Oral Oncol 1998; 34: 441-447.
4. Odgen GR. Alcohol and oral cancer. Alcohol 2005; 35: 169-173.
5. Braakhuis BJ, Visser O, Leemans CR. Oral and oropharyngeal cancer in the Netherlands between 1989 and 2006; Increasing incidence, but not in young adults. Oral Oncol 2009;45:e85-e89.
6. Leemans C, Braakhuis BJM, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011; 11: 9-22.
7. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002; 2: 342-349.
8. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra W, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison M. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24-35.
9. Syrjanen S, Lodi G, von B, I, Aliko A, Arduino P, Campisi G et al.. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Dis 2011; 17 Suppl 1:58-72.
10. Campbell BH, Mark DH, Soneson EA, Freije JE, Schultz CJ. The role of dental prostheses in alveolar ridge squamous cell carcinomas. Arch Otolaryngol Head Neck Surg 1997; 12:1112-1115.
11. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009; 45: 309-316.
12. Llewellyn CD, Johnson NW, Warnakulasuriya KAAS. Risk factors for squamous cell carcinoma of the oral cavity in young people- a comprehensive literature review. Oral Oncol 2001; 31: 401-418
13. Franceschi S, Barzan L, Talamini R. Screening for cancer of the head and neck: if not now, when? Oral Oncol 1997; 33: 313-316.
14. Waal van der I, de Bree R, Brakenhoff R, Coebergh JW. Early diagnosis in primary oral cancer: is it possible? Med Oral Patol Oral Cir Bucal 2011; 16(3):e300-e305.
15. Macpherson LMD, McCann MF, Gibson J, Binnie VI, Stephen KW. The role of primary healthcare professionals in oral cancer prevention and detection. Br Dent J 2003; 195:277-281.

16. Silverman S. Oral Cancer, Fourth edition American Cancer Society. B.C. Decker Inc. Hamilton. London 1998; 51-55.

17. Epstein JB, Güneri P: The adjunctive role of toluidine blue in detection of oral premalignant and malignant lesions. Curr Opin Otolaryngol Head Surg 2009; 17: 79-87.

18. Onofre MA, Sposto MR, Navarro CM. Reliability of toluidine blue application in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001; 91: 535-540.

19. Brinkmann O, Kastratovic DA, Dimitrijevic MV, Konstantinovic VS, Jelovac DB, Antic J et al.. Oral squamous cell carcinoma detection by salivary biomarkers in a Serbian population. Oral Oncol2011; 47: 51-55.

20. Xu GZ, Guan DJ, He ZY. 18FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. Oral Oncol 2011; 47: 560-565.

21. Krabbe CA, Pruim J, van der Laan BFAM, Rodiger LA, Roodenburg JLN. 18F-FDG PET and detection of distant metastasis and simultaneous tumors in head and neck squamous cell carcinoma: a comparison with chest radiography and chest CT. Oral Oncol 2009; 45: 234-240.

22. Broders AC. Squamous cell carcinoma of the lip. A study of five hundred and thirty-seven cases. JAMA 1920; 74: 656-664.

23. Pindborg JJ, Reichart PA, Smith CJ, van der Waal I. Histological typing of cancer and precancer of the oral mucosa. II ed. Berlin, Heidelberg, New York: Springer Verlag, 1997.

24. Anneroth G, Batsakis JG, Luna MA. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. Scand J Dental Res 1987; 95: 229-249.

25. Bryne M, Koppang HS, Lilleng R, Kjaerheim A. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol 1992; 166: 375-381.

26. Sawair F, Irwin CR, Gordon DJ, Leonard AG, Stephenson M, Napier SS. Invasive front grading: reliability and usefulness in the management of oral squamous cell carcinoma. J Oral Pathol Med 2002; 32: 1-9.

27. Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, Sutton D, Errington D, Vaughan D. Survival following primary surgery for oral cancer: A regional units experience in the UK. Oral Oncol 2009; 45: 201-2011.

28. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Oral Maxillofac Surg 2003; 32: 30-34.

29. McMahon J, O'Brien CJ, Pathak I, Hamill R, McNeil E, Hammersly N, Gardiner S, Junior E. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg 2003; 41: 224-231.

30. Weijers M, Snow GB, Bezemer PD, Wal van der JE, Waal van der I. The clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients. J Oral Pathol Med 2002; 31: 11-15.

31. Kurita H, Nakanishi Y, Nishizawa R, Xiao T, Kameta T, Koike T, Kobayashi H. Impact of different surgical margin conditions on local recurrence of oral squamous cell carcinoma. Oral Oncol 2010; 46: 814-817.

32. Slootweg PJ, Hordijk GJ, Schade Y, van Es RJJ, Koole R. Treatment failure and margin status in head and neck cancer. A critical view on the potential value of molecular pathology. Oral Oncol 2002; 38: 500-503.

33. Brandwein-Gensler M, Teixeira M, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Genden E, Urken ML, Wang BY. Oral squamous cell carcinoma. Histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. Am J Surg Pathol 2005; 29: 167-178.

34. de Carvalho AC, Kowalski LP, Marques Campos AHJ; Soares FA, Lopes Carvalho A, Vettore AL. Clinical significance of molecular alterations in histologically negative surgical margins of head and neck cancer patients. Oral Oncol 2012; 48: 240-248.

35. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009; 45: 309-316.

Table I. TNM classification of carcinomas of the lip and oral cavity

T –	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
T4a (oral cavity)	Tumor invades through cortical bone, into deep/ extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b (lip and oral cavity)	Tumor invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify tumor as T4.
N –	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension Note: Midline nodes are considered ipsilateral nodes.
M –	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1, T2 N1 M0 T3 N0, N1 M0
Stage IVA	T1, T2, T3 N2 M0 T4a N0, N1, N2 M0
Stage IVB	Any T N3 M0, T4b, Any N M0
Stage IVC	Any T, Any N M1

Ref: L.H. Sobin, M. Gospodarowicz, Ch. Wittekind (eds). TNM Classification of Malignant Tumours. 7th ed. New York: Wiley 2009.

Chapter 3

The Clinical Relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients

Weijers M. Snow GB, Bezemer PD, van der Wal JE, van der Waal I.

J Oral Pathol Med. 2002 Jan; vol. 31 (1) pp. 11-5

Abstract

Background: The clinical relevance of the presence of epithelial dysplasia in the margins of surgically removed oral squamous cell carcinoma is still unclear.

Method: In a retrospective study, the presence of mild or moderate epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma was examined histologically. Patients with tumor cells within 0.5cm of the surgical margins were excluded. Also patients with severe dysplasia were excluded, as this is usually regarded as carcinoma *in situ.* Patients that received postoperative irradiation were also excluded. Only patients who completed a follow-up period of five years were included. All together, a total number of 37 patients fulfilled the inclusion criteria.

Results: Epithelial dysplasia was observed in 7 out of 37 patients. Five of these patients, and two of the 30 patients with no dysplasia, had local recurrence ($p < 0.01$).

Conclusion: The presence of mild or moderate epithelial dysplasia in the margins of surgically removed oral squamous cell carcinoma carries a significant risk for the development of local recurrence. However, it should be noted that this study was of a retrospective nature and that the group of patients with epithelial dysplasia in the surgical margins was rather small. On the other hand, the inclusion criteria were somewhat strict, by limiting the oral subsite to tongue/floor of mouth, by excluding patients in whom tumor cells were found within 0.5cm of the surgical margins and by excluding patients who received postoperative radiotherapy, amongst others.

Introduction

The status of the surgical margins is an important prognostic factor in oral squamous cell carcinomas. A positive surgical margin not only results in a high risk of local recurrence (1-4), but also has a negative effect on the survival (3). The clinical relevance of the presence of epithelial dysplasia in the margins of a surgically removed oral squamous cell carcinoma is less clear. In general, epithelial dysplasia is considered to carry an increased risk of future malignant transformation.
The purpose of the present study was to investigate retrospectively the clinical relevance of epithelial dysplasia in the margins of surgically treated primary tongue and floor of mouth squamous cell carcinoma with regard to the development of local recurrence, observing a minimum follow-up period of five years.

Patients and Methods

Patients

The patients included in this study were drawn from the oncology data base of the Department of Oral and Maxillofacial Surgery/Oral Pathology and the Department of Otorhinolaryngology of the University Hospital Vrije Universiteit Amsterdam between January 1, 1985 and January 1, 1995.
Only patients diagnosed with a primary squamous cell carcinoma of the mobile tongue or floor of mouth (ICD-codes: C02.0, C02.1, C02.2, C04) were included, resulting in a total number of 176 patients. The TNM-classification of the UICC was used for staging of the tumors (5).
All patients underwent surgical treatment, with or without neck dissection. In general, a margin of 1 cm of mucosa with a clinically normal appearance was observed in the removal of the primary tumor. Thirty-one patients were excluded from the study because of immediate postoperative radiotherapy, re-excision of the primary tumor due to severe dysplasia/ carcinoma *in situ* or frank squamous cell carcinoma in the surgical margins, or insufficient histopathological material. As a result, 145 patients were included.

Histological material

After fixation, three to four mucosal margins, through the depth of the surgical specimen, were generally taken, with a width of approximately

0.2cm. Thereafter, one or more sections were taken through the central part of the tumor to facilitate evaluation of the deep surgical margins. The number of these central sections was dependent on the size of the tumor. The histological slides of the surgical mucosal margins and the deep surgical margins were revised. All slides were stained with Hematoxylin and Eosin (HE). The distance between the tumor cells and the margins was measured with an ocular micrometer.

Status of the surgical margin

WHO criteria were used for the assessment of epithelial dysplasia (6). No attempt was made to distinguish mild from moderate dysplasia. Severe dysplasia was regarded as carcinoma in situ and, as a result, was considered tumor positive; these patients had all underwent additional surgery, and were excluded from this study as indicated previously.

The status of the surgical margins was divided into four categories:

1. No tumor within 0.5 cm of the surgical margins and no epithelial dysplasia in the mucosal margins (47 patients)
2. No tumor within 0.5 cm of the surgical margins but presence of epithelial dysplasia in the mucosal margins (13 patients)
3. Tumor within 0.5 cm of the surgical margins and no epithelial dysplasia in the mucosal margins (63 patients)
4. Tumor within 0.5 cm of the surgical margins and presence of epithelial dysplasia in the mucosal margins (22 patients)

When tumor cells were observed within 0.5cm of the surgical margins, the patient was excluded from the study, irrespective of the presence or absence of epithelial dysplasia in the mucosal margins. As a result, categories 3 and 4 were excluded, this study being limited to patients in category 1 and 2, and totalling 60 patients.

Local recurrence

Local recurrence was defined as tumor development at the site of the primary tumor, independent of the time interval after the treatment of the primary.

Follow-up

In this study a follow-up period of five years was observed. Three patients were excluded because of non-compliance in completing the follow-up period. Apart from the patients who had been excluded because

of immediate postoperative radiotherapy, also patients who received radiotherapy in the head and neck region at a later stage during the follow-up period were also excluded from the study. As a result, another 14 patients were excluded. Six patients were also excluded because of death from other causes within five years. This left a total of 37 patients: 30 patients in group 1 and 7 patients in group 2. The exclusion criteria have been summarised in table 1.

Table 1. Exclusion criteria in patients (n=176) treated surgically for a primary squamous cell carcinoma of the tongue and floor of the mouth between 1985 and 1995

	No. of patients
• Immediate reexcision because of insufficient margins, including the presence of severe dysplasia/carcinoma in situ in the mucosal margins; immediate postoperative irradiation or irradiation during follow-up. Insufficient histologic material for reevaluation	31
• Tumor cells within 0.5 cm of the surgical margins	85
• Incomplete five-year follow-up period, including death of other causes	9
• Irradiation at a later stage during follow-up	14
• Number of patients included in this study	37

Smoking habits

Smoking habit was available for all but one patient. For the purpose of this study, the patients were categorised either as a non-smoker or a smoker at the time of surgery, without an attempt to subdivide the latter group in mild, moderate or heavy smokers. There were 29 smokers, 7 non-smokers and one patient where smoking habit was unknown. No reliable data could be found regarding the possible cessation of smoking habits, if applicable, after the surgical treatment of the primary tumor. No reliable data were available about alcohol consumption either.

Statistical methods

The Fisher exact test was used to examine the significance of the presence or absence of epithelial dysplasia in the surgical margins with regard to the development of local recurrence.

Results

Local recurrence occurred in 2 out of 30 patients from group 1 and in 5 out of 7 patients from group 2, the difference being statistically significant ($p<0.01$) (Table 2). Recurrences occurred from 9 months to 44 months after surgery of the primary. There was no statistically significant difference between smokers and non-smokers with regard to the development of local recurrence (Table 3).

Table 2. Local recurrence in dysplastic and nondysplastic surgical margins*

	No local recurrence	Local recurrence	Total
No dysplasia (group 1)	28	2	30
Dysplasia (group 2)	2	5	7
All patients	30	7	37

* $p<0.01$

Table 3. Local recurrence in smokers and nonsmokers (Groups 1 and 2; n=37)

	Smokers	Non-smokers	Unknown	All patients
Local recurrence	6	1	-	7
No local recurrence	23	6	1	30
All patients	29	7	1	37

$p=0.7$ (n.s.)

Discussion

Primary squamous cell carcinoma of the tongue or floor of mouth was focused on in the present study because these subsites are the most common ones in oral cancer. Furthermore, the surgical approach to carcinomas in these subsites is more or less similar.

Patients who received direct or "delayed" postoperative radiotherapy, particularly because of nodal disease in the neck, were excluded since the primary site is usually included in the field of irradiation.

There are no uniformly accepted criteria for the assessment of tumor free margins in surgically excised squamous cell carcinoma of the oral mucosa. A distance of 0.5 cm between the tumor cells and the surgical margin, as

being defined in this study, seems an acceptable one and has been used by others (3, 4, 7). Nevertheless, the distance used may also depend on growth pattern: in a tumor growing in a more or less solid fashion, the reliability of a tumor free margin of 0.5 cm is probably higher than in a tumor in which the tumor grows in small nests and cell groups.

Of course, the representativeness of the sections studied is a problem, with regard to assessment of the radical nature of the tumor and the assessment of the presence or absence of epithelial dysplasia in the mucosal margins. Therefore, some of the local recurrences observed in the present study may have been due to insufficiently wide surgical margins and not to the presence of epithelial dysplasia in the mucosal margins. At the same time, local recurrences in patients in the absence of epithelial dysplasia in the mucosal margins may perhaps be explained by the presence of epithelial dysplasia that was not included in the histological sections studied. Furthermore, there is some degree of subjectiviness in the assessment and grading of epithelial dysplasia, which may have influenced the composition of the present study groups.

Based on a small group of patients, studied retrospectively, the pattern of p53 immunoexpression in the surgical margins of oral squamous cell carcinoma seems to be of predictive value for the future development of local recurrence (8).

This may justify routine examination of all patients with no epithelial dysplasia in the mucosal margins, as assessed by light microscopic examination. In another study of 25 head-and-neck cancer patients with negative histopathological margins, p53 mutation was observed in 13 of them, and 5 had a local recurrence, while no such event occurred in the remaining 12 (9). A somewhat similar experience was observed in a group of 18 patients with oral squamous cell carcinoma (10). Field cancerization, in the explanation of local recurrence in the prescence of histologically negative margins, has received much attention. A recent paper showed that field cancerization was due to multiple independent events rather than migration of genetically altered cells (11).

In the present study there was no significant difference in the presence or absence of epithelial dysplasia in men compared to women (Table 4). Furthermore, no significant difference was found between the presence or absence of epithelial dysplasia in the tongue compared to the floor of the mouth (Table 5). Also there was no real correlation with T-stage and presence or absence of epithelial dysplasia in the mucosal margins (Table 6).

The finding that local recurrences are significantly more common in the presence of dysplasia in the mucosal margins is more or less in consistent with what is known about the risk of malignant transformation of oral leukoplakia. There, too, the risk of malignant transformation is significantly higher in the presence of epithelial dysplasia in comparison with leukoplakias in which no dysplasia is found at histological examination. Although occasionally a squamous cell carcinoma will develop in non-dysplastic oral leukoplakia. It is also well known that epithelial dysplasia in oral leukoplakia does not always result in malignant transformation, although the length of the follow-up period should be taken into account when considering such instances. Interestingly, it has recently been shown that the nuclear DNA content in dysplastic cells is of stronger predictive value, with regard to malignant transformation in oral leukoplakia, than the degree of dysplasia (12).

Local recurrence has been defined as development of tumor at the site of the previously removed squamous cell carcinoma in this study, independent of the time interval. One could perhaps defend the hypothesis that a time interval of less than two years would concur with the concept of a local recurrence, while tumor growth at the site of the previously removed squamous cell carcinoma over a longer time interval, could be regarded as a second primary. However, such distinction seems to be of academic interest only.

Tobacco habits do not seem to play a significant role in local recurrence (Table 6), although the small number of patients with epithelial dysplasia (n=7) does not allow statistical comparison of the possible role of smoking habits in patients with and without epithelial dysplasia and local recurrence.

In conclusion, in the absence of epithelial dysplasia in the mucosal surgical margins and in the absence of tumor cells within 0.5cm of the other surgical margins, local recurrence after treatment of a primary squamous cell carcinoma of the tongue or the floor of the mouth occurs in less than 7% during the follow-up period of five years. However, when mild or moderate epithelial dysplasia is present in the mucosal margins, the chance of local recurrence within five years after surgical removal of the primary may well be over 50%. Immediate reexcision, if feasible, should therefore be considered. The present study did not include patients in whom severe dysplasia/carcinoma *in situ* was found in the surgical margins, as those patients were all treated by immediate reexcision.

Table 4. Male - female distribution and presence of epithelial dysplasia

	No dysplasia	Dysplasia	Total
Male (mean age 61.4 yrs)	14	5	19
Female (mean age 61.7 yrs)	16	2	18
Total	30	7	37

Table 5: Site distribution and presence of epithelial dysplasia

	No dysplasia	Dysplasia	Total
Tongue	14	5	19
Floor of mouth	16	2	18
Total	30	7	37

Table 6: T-stage and presence of epithelial dysplasia

	No dysplasia	Dysplasia	Total
T1	7	5	12
T2	13	2	15
T3	9	-	9
T4	1	-	1
Total	30	7	37

References

1. Jones K, Lodge-Rigal R, Reddick R, Tudor G, Schockley W. Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. *Arch Otolaryngol Head Neck Surg* 1992; 118: 483–5.

2. Ravasz L, Slootweg P, Hordijk G, Smit F, Tweel van der I. The status of the surgical margin as a prognostic factor in the treatment of head and neck carcinoma. *J Cranio Max Fac Surg* 1991; 19: 314–8.

3. Looser K, Shah J, Strong E. The significance of 'positive' margins in surgically resected epidermoid carcinomas. *Head Neck Surg* 1978; 1:107–11.

4. Loree T, Strong E. Significance of positive margins in oral cavity squamous carcinoma. *Am J Surg* 1990; 160: 410–4.

5. Sobin LH, Wittekind Ch. TNM Classification of Malignant Tumours, 5th edn. UICC, Wiley-Liss, Inc.: New York, 1997: 20–4.

6. World Health Organization Collaborating Centre for Oral Precancerous Lesions. Definition of leukoplakia and associated lesions: an aid to studies on oral precancer. *Oral Surg Oral Med Oral Pathol* 1978; 46:518–39.

7. Lumermann H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 79: 321–9.

8. Cruz I, Meijer C, Snijders P, Snow G, Walboomers J, Waal van der I. p53 immunoexpression in oral carcinogenesis: potential consequences for clinical management. *J Pathol* 2000; 191: 132–7.

9. Brennan JA, Mao L, Hruban RH, et al. Molecular assessment of histopathological staging in squamous-cell carcinoma of the head and neck. *N Engl J Med* 1995; 332: 429–35.

10. Partridge M, Li S-R, Pateromichelakis S, et al. Detection of minimal residual cancer to investigate why oral tumors recur despite seemingly adequate treatment. *Clin Cancer Res* 2000; 6: 2718–25.

11. Oijen van MGCT, Slootweg PJ. Oral field cancerization: carcinogen-induced independent events or micrometastatic deposits? *Cancer Epidemiol, Biomarkers Prevention* 2000; 9: 249- 56.

12. Sudbö J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. *N Engl J Med* 2001; 344: 1270–8.

Chapter 4

The status of the deep surgical margins in tongue and floor of mouth squamous cell carcinoma and risk of local recurrence; an analysis of 68 patients

Weijers M, Snow GB, Bezemer PD, van der Wal JE, van der Waal I.

Int J Oral Maxillofac Surg. 2004 Mar; vol. 33 (2) pp. 146-9

Abstract

The objective of this study is to retrospectively assess the clinical relevance i.c., the event of a local recurrence, in patients surgically treated for tongue and floor of mouth squamous cell carcinoma when tumor cells are observed histopathologically at a distance of less than 0.5 cm of the deep surgical margin. Furthermore, the pattern of invasion and the presense or absence of perineural spread were recorded. A total of 68 patients, surgically treated because of a tongue or floor of mouth squamous cell carcinoma, were examined. Patients in whom any degree of epithelial dysplasia was observed in the mucosal margins surgical had been excluded beforehand.

Local recurrence occurred in 2 out of 30 patients with a free surgical margin >0.5cm and in 3 out of 38 patients with a free surgical margin ≤0.5 cm, the difference being not statistically significant. Apparently, the presence of tumor cells within a distance of less than 0.5 cm, but not into the deep surgical margin, does not necessarily seem to require additional treatment. The pattern of invasion and the presence or absence of perineural spread were not significantly related with local recurrence either.

Introduction

In oral squamous cell carcinomas, surgery is one of the most important treatment options.

The status of the surgical margins is an important prognostic factor. Positive surgical margins, with tumor cells within the margin, not only result in a high risk of local recurrence, (1-4) but also has a negative effect on the survival (3). Because of those risks, surgical therapy aims at obtaining 'free' surgical margins. However, the precise 'safe' distance between the tumor cells and the surgical margin remains unclear.

The purpose of the present study was to investigate, retrospectively, the clinical relevance of the distance of the tumor cells to the deep surgical margins of primary tongue and floor of mouth squamous cell carcinoma with regard to the development of local recurrence. The relevance of epithelial dysplasia in the mucosal margins has been published elsewehere (5).

Materials and Methods

The patients included in this study were drawn from the oncology database of the Department of Oral and Maxillofacial Surgery/Oral Pathology and the Department of Otorhinolaryngology of the University Hospital Vrije Universiteit University Medical Center, Amsterdam in the period 1 January 1985 and 1 January 1995.

Only patients diagnosed with a primary squamous cell carcinoma of the mobile tongue or floor of mouth (ICD-codes: C02.0, C02.1, C02.2, C04) were included, resulting in a total number of 176 patients. For the staging of the tumors, the TNM-classification of the UICC was used (6).

All patients underwent surgical treatment, with or without neck dissection. Sixty-six patients were excluded from the study because of various degrees of epithelial dysplasia in the mucosal margins; severe dysplasia was regarded synonymous as carcinoma. Furthermore, patients were excluded because of immediate radiotherapy or reexcision because of positive margins. As a result, 110 patients were included of whom the deep surgical margins were free of tumor, being defined as no tumor cells present in the inked margin.

All histological slides of the surgical margins were revised without being informed about the clinical course. In our Department of Pathology, the protocol for the gross sectioning of the surgical specimen prescribes a

fixation period of at least 24h and the inking of the entire surgical surface with Indian ink. The lateral margins are taken first, followed by lamellation of the remaining specimen. The thickness of these lateral sections is usually in the range of 0.2-0.3 cm. Usually more than one section is taken from the central part of the tumor. In the present study, the deepest slide was included for the measurements. The distance between the tumor cells and the deep surgical margins was measured with an ocular micrometer.
The status of the deep surgical margins was divided into two categories;
1. No tumor within 0.5 cm (> 0.5 cm) of the surgical margin (47 patients).
2. Tumor within 0.5 cm (≤ 0.5 cm) of the surgical margins (63 patients).
The division in absence of tumor within 0.5cm ('clear margin') and presence of tumor within 0.5cm of the margin ('close margin') is in accordance with the proposal by Bataskis et al, and Sutton et al (7,8).
The histologic pattern of tumor invasion was divided in a semiquantitative way into three categories: 1 pushing borders or solid infiltrating tumor cells, 2 small groups of infiltrating tumor cells, and 3 widespread dissociation of tumor cells. Furthermore, the presence or absence of perineural spread was recorded.
Local recurrence was defined as tumor development at the site of the primary tumor, independent of the time interval after the treatment of the primary.

A follow-up period of 5 years was observed. Four patients were excluded because of non-compliance. Patients who received radiotherapy in the head and neck region during the follow-up period were excluded from the study. A total of 18 patients (9 in category 1 and 9 in category 2) were excluded for this reason. Twenty patients were excluded (5 patients in category 1 and 15 patients in category 2) because of death of other causes within five years. As a result, a total of 68 patients have been studied: 30 patients in category 1 and 38 patients in category 2. The data of these 68 patients are summarised in tables 1-3. The exclusion criteria have been summarised in table 4.

The Fisher exact test was used to examine the significance of the surgical margins >0.5 cm (category 1) and ≤ 0.5 cm (category 2) with regard to the development of local recurrence.

Table 1. Male - female distribution and state of deep surgical margin (n=68)*

Patients	Mean age	Margin (>0.5cm)	Margin (≤ 0.5cm)	Total
Male	57.7 Y	19	24	43
Female	58.5 Y	11	14	25
Total	58.0 Y	30	38	68

*ns (p> 0.01)

Table 2. Site distribution and state of deep surgical margin (n=68)*

Site	Margin (>0.5cm)	Margin (≤ 0.5cm)	Total
Tongue	14	17	31
Floor of mouth	16	21	37
Total	30	38	68

*ns (p> 0.01)

Table 3. T-stage and status of deep surgical margin (n=68)*

T-stage	Margin (>0.5cm)	Margin (≤ 0.5cm)	Total
T1	7	13	20
T2	13	23	36
T3	9	2	11
T4	1	-	1
Total	30	38	68

*p<0.01 for T1/T2 stages compared with T3/T4

Table 4. Exclusion criteria in patients treated surgically for a primary squamous cell carcinoma of the tongue and floor of the mouth (n=176)

Exclusion criteria	No. of patients
* Various degrees of epithelial dysplasia in the mucosal margins; Immediate reexcision or postoperative radiotherapy because of positive margins	66
* Incomplete five-year follow-up period, including death of other causes	24
* Irradiation at a later stage during follow-up	18
* Total number of excluded patients	108

Results

Local recurrence occurred in 2 out of 30 patients from category 1 and in 3 out of 38 patients from category 2, the difference being not statistically significant (p>0,01) (Table 5). Recurrences occurred in a range from 2 months to 29 months after surgery of the primary.
The pattern of invasion of the tumor cells was more or less similar in groups 1 and 2 ; local recurrences were equally distributed as well between groups 1 and 2 (Table 6). Perineural spread was not significantly associated with local recurrence and was equally distributed among the patients of groups 1 and 2 (table 7).

Table 5. Local recurrence in patients with deep surgical margins >0.5 cm and margins ≤ 0.5 cm*

Free Margin	Local recurrence	No local recurrence	Total
> 0.5 cm	2	28	30
≤.05 cm	3	35	38
Total	5	63	68

*ns (p> 0.01)

Table 6. Pattern of invasion and local recurrences (n=68)*

	No. of patients	Local recurrences		No local recurrences	
Pattern of invasion	(*n*=68)	Group 1 (*n*=30)	Group 2 (*n*=38)	Group 1 (*n*=30)	Group 2 (*n*=38)
Pushing borders or solid infiltrating tumor cells	9	-	-	5	4
Small groups of infiltrating tumor cells	49	-	3	20	26
Wide spread dissocation of tumor cells	10	2	-	3	5

*ns (*P*>0.01)

Table 7. Perineural spread and local recurrence (n=68)*

	No. of patients	Local recurrences		No local recurrences	
Perineural spread	(*n*=68)	Group 1 (*n*=30)	Group 2 (*n*=38)	Group 1 (*n*=30)	Group 2 (*n*=38)
Present	9	1	-	4	4
Absent	59	1	3	24	31

*ns (*P*>0.01)

Discussion

The justification to focus the present study on primary squamous cell carcinoma of the tongue or floor of mouth was based on the fact that these subsites are the most common ones in oral cancer. Furthermore, the surgical approach of carcinomas in these subsites is more or less similar. Patients with various degrees of epithelial dysplasia in the mucosal margins have been excluded from this study, since it would be actually impossible to identify the cause of recurrence being either due to progression from epithelial dysplasia or to incomplete removal.
The distribution of tumor cells at a distance of less than 0.5 cm and a distance of more than 0.5 cm in this excluded group showed to be similar as in the included patients group. The same aplies to the excluded patiens who died within 5 years because of other causes.
Patients who received direct or "delayed" postoperative radiotherapy, particularly because of nodal disease in the neck, were excluded since the primary site is usually included in the field of irradiation and, thus, may have influenced the risk of local recurrence. It is unlikely that the exclusion of this group of patients has caused a bias with regard to the distribution of the two study groups, being tumor cells at a distance of less than 0.5 cm and of more than 0.5 cm.
There are no uniformly accepted histopathological criteria for the assessment of tumor free margins in surgically excised squamous cell carcinoma of the oral mucosa. A distance of 0.5 cm between the tumor cells and the deep surgical margin, as being defined in this study, has also been used by others (2,3,9). Interestingly, in the present study, no significant difference was found between the categories with tumor cells at a distance of less than 0.5 cm and a distance of more than 0.5 cm from the deep margin with regard to the development of local recurrence. In

further studying group 2 (tumor at a distance of less than 0.5 cm) four patients were observed with tumor not truly into the margin but at a distance of approximately 0.1 cm; none of these patients developed a local recurrence during the 5-year follow-up period. Of the three patients of group 2 who did develop a recurrence, closeness of tumor cells to the deep surgical margin was 0.13 cm, 0.41 cm and 0.44 cm respectively. Therefore, the need for subdividing the group of patients with tumor cells present at a distance of less than 0.5 cm into subgroups, e.g. less than 0.1 cm, 0.1-0.3 cm and 0.3-0.5 cm seems questionable. Local recurrences in our group can not be explained by the possible presence of epithelial dysplasia in the mucosal resection margins since those patients had been excluded.

In order to obtain tumor free margins, it is important to take the shrinkage of tumor tissue into account. Apparently the tumor tissue shrinks after resection and during the preparation of the slides. Johnson et al, studied the amount of tissue shrinkage in mongrel dogs (10). They found that the deep tongue margin shrank almost 34.4%. Their advise to obtain a pathologically clear margin of 0.5 cm was to take an surgical *in-situ* margin of at least 0.8-1.0 cm, what is indeed common practice.

Our protocol of gross sectioning of the surgical specimen (taking the lateral margins first, followed by lammelation of the remaining specimen results in a rather accurate information of tumor extension in the vertical dimension (deep surgical margins) but less so into the horizontal dimension (lateral surgical margins).

Remarkably, our patients with T3/T4 tumors more often showed tumor free margins than patients with T1/T2 tumors (table 3). This difference was statistically significant. An explanation for this finding might be the fact that surgeons tend to excise larger tumors more aggressively than small ones.

Looser et al, in their study found a great number of local recurrences in patients with tumor cells within 0.5 cm distance of the margin (2). However, their study was based on different sites within the head and neck region and some patients received preoperative radiotherapy.

Hicks et al, found a much lower local control rate in patients with margins < 0.5 cm (11). However, no distinction was made between positive margins and margins < 0.5 cm. This was also the case in the study of Al-Raji et al, in which the recurrence free survival percentage was much higher in patients with margins < 0.5 cm, but in their study, too, patients with

positive margins were included (9). A factor that might have influenced the outcome of the present study is the way of categorizing the patients; the dichotomy was somewhat arbitrarily set at 0.5 cm.

The significance of the distance between the tumor cells and the deep surgical margin may also be dependent on the pattern of invasion of the tumor and the presence or absence of perineural spread. Apparently, this was not the case in the present study, nor with regard to the pattern of invasion neither with regard to the presence of perineural spread (12).

In conclusion, the histopathological demonstration of tumor cells within a distance of less than 0.5 cm, but not into the deep surgical margins, does not necessarily seem to require additional treatment.

References

1. Jones K, Lodge-Rigal R, Reddick R, Tudor G, Shockley W. Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. Arch Otolaryngol Head Neck Surg 1992;118:483-485.

2. Looser K, Shah J, Strong E. The significance of 'positive' margins in surgically resected epidermoid carcinomas. Head Neck Surg 1978;1:107-111.

3. Loree T, Strong E. Significance of positive margins in oral cavity squamous carcinoma. Am J Surg 1990;160:410-414.

4. Ravasz L, Slootweg P, Hordijk G, Smit T, van der Tweel I. The status of the surgical margin as a prognostic factorin the treatment of head and neck carcinoma. J Craniomaxillofac Surg 1991;19:314-318.

5. Weijers M, Snow GB, Bezemer PD, van der Wal JE, van der Waal I. The clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients. J Oral Pathol Med 2002;31:11-15.

6. Sobin LH, Wittekind Ch. TNM Classification of Malignant Tumours, 5th edn. UICC, Wiley-Liss, Inc.: New York, 1997:371.

7. Batsakis JG. Surgical excision margins: a pathologist's perspective. Adv Anat Pathol 1999;6:140-148.

8. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2003;32:30-34.

9. Al-Rajhi N, Khafaga Y, El-Husseiny J. Early stage carcinoma of oral tongue : prognostic factors for local control and survival. Oral Oncol 2000;36:508-514.

10. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. Head Neck 1997;19:281-286.

11. Hicks WL, Loree TR, Garcia RI, Maamoun S, Marshall D, Orner JB, Bakamjian VY, Shedd DP. Squamous cell carcinoma of the floor of mouth: A 20-year review. Head Neck 1997;19:400-405.

12. van Es RJ, van Nieuw Amerongen N, Slootweg PJ, Egyedi P. Resection margin as a predictor of recurrence at the primary sitefor T1 and T2 oral cancers. Arch Otolaryngol Head Neck Surg 1996;122:521-525.

Chapter 5

Malignancy grading is not better than conventional histopathologic grading in small squamous cell carcinoma of tongue and floor of mouth; retrospective study in 128 patients

Weijers M, Snow GB, Bezemer PD, van der Waal I.

J. Oral Pathol. Med. 2009 Apr; vol. 38(4) pp. 343-7

Abstract

There is an ongoing debate about the predictive value of histopathological parameters in oral cancer. In the past decades, the emphasis has been on the possible added value of the so-called malignancy grading system. In a retrospective study on 128 previously untreated patients with a T1 or T2 squamous cell carcinoma of the tongue and the floor of the mouth the value of the classical Broders' grading system and the malignancy grading system were compared with regard to various outcome measures such as regional metastasis, local recurrence and 5-year survival.
The results show that neither histological grading system has a strong predictive value and that none is superior to the other.

Introduction

There are several clinical and histopathological parameters which are used to assess the prognosis of oral squamous cell carcinoma. The prognostic value of the TNM-classification system is rather limited (1-4). Therefore, other parameters have been investigated, particularly histopathological ones. The most commonly used histopathological grading system is the one introduced by Broders (5) and modified by the WHO (6). However, its prognostic value seems questionable. In the late 1980's, a more detailed histopathological grading system has been introduced, referred to as malignancy grading system. Apart from the degree of keratinization, nuclear polymorphism and number of mitoses also parameters of the tumorhost relationship, such as pattern of invasion, stage of invasion and density of the tumor related lymphoplasmacytic infiltration, are included in this system (7-9). Several studies have shown the predictive value of this malignancy grading system with regard to the occurrence of late cervical metastases (10-13).
The purpose of the present study was to investigate the prognostic value of histopathological parameters in squamous cell carcinomas of the tongue and floor of the mouth, as expressed in 5-year survival rate and first event such as local recurrence, regional metastases and second primary tumors. The parameters that have been applied are the histological grade of differentiation according to Broders and the malignancy grading system according to Anneroth et al. (7) Furthermore, perineural and angiolymphatic invasion were studied. The state of the resection margins with regard to local recurrence has been discussed in previous reports (14, 15).

Patients and Methods

Patient material

A group of consecutive patients surgically treated, with or without elective neck dissection, for a primary squamous cell carcinoma of the tongue or floor of the mouth (ICD-codes: C02.0,1,2/C04) at the Vrije Universiteit Medical Centrum (VUmc) in Amsterdam between January 1985 and January 1995 were studied. The tumor stages were limited to stage I and II. Patients were excluded from the study in case of previous malignancies in or outside the oral cavity, immediate reexcision of the primary tumor,

and postoperative radiotherapy. Patients were also excluded from the study in case of tumor cells within the resection margins and/or positive lymph nodes. As a result, 128 patients were included.
For the staging of the tumors, the TNM-classification of the UICC 2002 was used (16).
The following events were registered: local recurrence, regional metastases, and the development of a second primary tumor in or outside the head and neck region. The minimum followup period was five years.
Local recurrence was defined as tumor development within 2 years at the site of the primary tumor. A second primary was defined as tumor development at a different subsite than that of the primary tumor, irrespective of the time interval or at the site of the primary tumor at least 2 years after removal of the primary tumor. Neck node metastases were defined as cytologically or histologically proven presence of squamous cell carcinoma in one or more lymph nodes. The demographic data and data on treatment are shown in table 1.
The occurrence of first events was as follows; 29 patients (23%) had regional metastasis, 13 patients (10%) had a local recurrence, and 6 patients (5%) developed a primay tumor in the oral cavity or oropharynx. The overall 5-year survival rate was 67%; 11% of the patients died of their oral cancer. Four percent were alive with evidence of disease, 7% died of second primary cancer and 11% died of other causes.

Table 1. Demographic data of 128 patients (tongue 67; floor of mouth 61)

Male	82
Female	46
Male-female ratio	1.8
Mean age (yrs)	62 (range 37-87)
Stage I	63
Stage II	65
Local treatment	86
Local treatment and elective neck dissection	42

Histopathology
For the purpose of the study, re-assessment of the original slides was performed by an oral pathologist (IvdW). The pathologist was not aware of the original report of the slides or the identitiy of the patient. In our

department of pathology, the protocol for the gross sectioning of the surgical specimen prescribes the taking of the lateral margins followed by lamellation of the remaining specimen. Usually, more than one section is taken from the central part of the tumor. In the present study, all sections were re-assessed.

Table 2. Broders' grade in 128 patients

Broders' grade	Number of patients
I	42
II	83
III	3
Total	128

Broders' grading was performed on the entire tumor mass and the results are shown in table 2. The malignancy grading was performed at the forefront of the tumor according to the system of Anneroth et al. (7) The total malignancy score according to the system of Anneroth was divided into four groups: (i) score 12 and below (n=26 20%), (ii) score 13 (n=36 28%), (iii) score 14 (n=44 34%), and (iv) score 15 and higher (n=22 17%). The scores for each histopathological item are shown in table 3; the distribution of the total malignancy score is shown in figure 1.
Perineural invasion was defined as infiltration of the perineural space by tumor cells. This feature was assessed within the whole tumor. This phenomenon was present in 13 patients (10%), absent in 114 (89%) and not assessable in one patient (1%). Angiolymphatic invasion was defined as the presence of aggregates of tumor cells within endothelial-lined channels or invasion of the media of a vessel with ulceration of the overlying intima. No distinction was made between blood vessels and lymphatic vessels. For this purpose Elastica von Gieson stains were examined. Angiolymphatic invasion was present in 12 patients (9%), absent in 112 patients (89%) and not assessable in 4 patients (2%).

Table 3. Distribution of the different parameter scores of the malignancy grading system in 128 patients

Parameter	Score	Number of patients
Degree of keratinisation	1	7
	2	108
	3	13
	4	-
Nuclear polymorphism	1	5
	2	119
	3	4
	4	-
Number of mitosis	1	102
	2	25
	3	1
	4	-
Pattern of invasion	1	1
	2	17
	3	95
	4	15
Stage of invasion	1	-
	2	5
	3	50
	4	73
Lymphoplasmacytic infiltration	1	47
	2	69
	3	11
	4	1

Statistical analysis

Percentages were compared with the Chi square test (except for the smaller groups). $P < 0.05$ were considered as indicating statistical significance.

Results

Limiting the Broders' system to grades 1 and 2, there was no significant difference in differentiation and occurrence of the various first events

(table 4, p-values > 0.25). There was no significant difference either in survival between the patients with well differentiated and moderately differentiated tumors (table 5, p-values > 0.20). Because of the small number of patients with grade 3, these have not been included in the analysis.

Using the malignancy grading system of Anneroth, there was no difference in the occurrence of the various first events between the four groups (table 6, p-values > 0.15) . There was no statistically significant difference in survival between patients with low and high malignancy scores either (table 7, p-values > 0.50). None of the parameters of the malignancy grading system was statistically shown to have more predictive value than the others.

A tendency was seen that in patients with regional metastases growth in vessels was more common; there was also a tendency that perineural spread was more common in patients who died of their oral cancer. However, both findings were not statistically significant.

Figure 1 Distribution of total malignancy scores in 128 patients

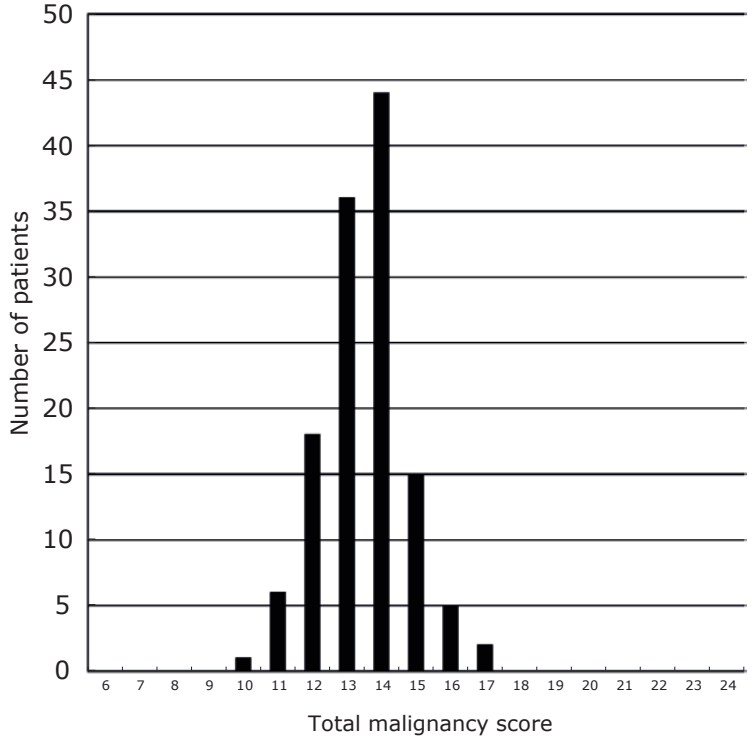

Table 4. Broders' grade and first event; no significant differences

Broder's grade	I	II	III*	All grades
Disease free after 5 years	24	39	3	66
Regional metastases	10	19	-	29
Local recurrence	3	10	-	13
2nd Primary oral cavity or oropharynx	1	5	-	6
2nd Primary elsewhere	4	7	-	11
Death of other causes	-	3	-	3
Total number of patients	42	83	3	128

* Not included in the analysis because of small number of patients

Table 5. Broders' grade and patient status at five-year of follow-up; no significant differences

Broder's grade	I	II	III*	All grades
Alive no evidence of disease	31	52	3	86
Alive evidence of disease	-	5	-	5
Death of disease	5	9	-	14
Death of other causes	3	11	-	14
Death of 2nd primary	3	6	-	9
Total number of patients	42	83	3	128

* Not included in the statistical analysis because of small number of patients

Table 6. Total malignancy score and first event; no significant differences

					Total number of patients
Total malignancy score	-12	13	14	15-	128
Disease free	18	18	18	12	66
Regional metastases	3	10	10	6	29
Local recurrence	2	3	7	1	13
2nd Primary oropharynx	-	1	4	1	6
2nd Primary elsewhere	2	3	4	2	11
Death of other causes	1	1	1	-	3
Total number of patients	26	36	44	22	128

Table 7. Total malignancy score and patient status end of follow up; no significant differences

					Total number of patients
Total malignancy score	-12	13	14	15-	128
Alive no evidence of disease	19	21	30	16	86
Alive evidence of disease	-	1	3	1	5
Death of disease	1	5	6	2	14
Death of other causes	3	5	4	2	14
Death of 2nd primary	3	4	1	1	9
Total number of patients	26	36	44	22	128

Discussion

The present study was deliberately restricted to patients with small squamous cell carcinoma of the tongue and floor of the mouth without lymph node metastases to assess reliably the prognostic value of histopathological parameters with regard to local recurrence, regional metastasis and 5-year survival. For the same reasons, patients who received post-operative radiotherapy have been excluded. To the best of our knowledge, no comparable selection criteria have been used in other papers on this subject.

Bryne et al. compared Broders' grading system with the malignancy grading system according to Anneroth and found no prognostic value for Broders grading, whereas the malignancy grading system according to Anneroth did. (8) In contrast to our study, Odell et al. found that a less differentiated Broders' grade correlated with an increased risk of local recurrence (9). Keski-Santti et al. studied different histopathological parameters (mode of invasive front, pattern of invasion, histological grade and depth of invasion (measured in mm) (17). Their outcome was, like in the present study, that none of the individual parameters of the malignancy grading system had prognostic significance with respect to survival. The measured depth of infiltration and p-T stage predicted occult cervical metastasis; p-T stage also predicted local recurrences. It should be mentioned that the study by Keski-Santti et al. was limited to stages I and II, as in the present study, but only included carcinomas of the tongue.

Woolgar et al., applying the malignancy grading system, concluded that the degree of keratinisation, mitotic figures and pattern of invasion did have a significant value in predicting metastases (18). Many investigators omitted the feature 'number of mitoses', because of interobserver disagreement, tumor heterogeneity and variations in the high power fields between different microscopes (9, 19, 20). Woolgar et al. found that the frequency of mitotic figures was significantly higher in patients with regional metastases (18). In the present study, this observation could not be confirmed. In 1999 Woolgar found a correlation between histological malignancy grade (HMG) and the occurrence of lymph node metastases (21). A correlation was found between HMG and survival.

Amaral et al. studied the predictive factors of occult metastasis and prognosis of stage I and II carcinoma of the tongue and floor of the mouth (22). They found that muscular infiltration was associated with the presence of occult metastasis. This factor was also associated with disease free survival.

In a study by Kurokawa et al., using the malignancy grading system, a high prognostic value of the histological grade in the deep invasive front of tongue squamous cell carcinoma was observed (23). It is difficult to comment on those findings, since also patients with stage III and stage IV had been included. Besides, probably a number of these patients have received postoperative radiotherapy.

Vascular and perineural invasion were studied because of their possible prognostic value with regard to cervical metastasis. Poleksic et al. (24), Shingaki et al. (25), Brown et al. (26), Woolgar et al. (18, 21) and Yuen et al. (27) found a significant prognostic value for perineural invasion with regard to local recurrence. Woolgar et al. found in their study that both vascular and perineural invasion had significant independent value in predicting nodal metastases (18). Like in the present study, no attempt was made to distinguish between lymphatic and blood vessels. Fagan et al. also found that perineural invasion was associated with an increased risk of local recurrence and cervical metastases (28). In their study, Sutton et al. found that the presence of perineural spread and/or vascular invasion was strongly related to close or involved margins (29). McMahon et al. found that local recurrence was predicted by the presence of perineural invasion (30). This is not in accordance with the results of the present study. Finally, Amaral et al. found that the presence of vascular invasion was associated with occult metastasis in tongue tumors (22). As mentioned before, there

is no similary designed study reported in the literature that would allow comparison with the present results. Furthermore, it is well recognized that stage I and II oral squamous cell carcinomas have a relatively good prognosis and that any grading or scoring system may be too crude to be of value in such select group.

Conclusion

In the present study, no significant predictive value for Broders' system and the malignancy grading system of Anneroth was found in T_1N_0 and T_2N_0 squamous cell carcinomas of the tongue and the floor of the mouth. Because P-values are high, this cannot be explained by lack of power. Tumor growth in vessels tend to be a risk factor for regional metastasis, but not at a significant level. The same applies to perineural spread with regard to poor survival.

At present, no biological markers are available that have shown to be of more prognostic value than the traditional histopathologic parameters.

References

1. Anneroth G, Batsakis JG, Luna M. Malignancy grading of squamous cell carcinoma in the floor of the mouth related to clinical evaluation. Scand J Dent Res 1986 94: 347-56.

2. Gluckman JL, Pavelic ZP, Welkoborsky HJ, Mann W, Stambrook P, Gleich L, Wilson K. Prognostic indicators for squamous cell carcinoma of the oral cavity: a clinicopathologic correlation. Laryngoscope 1997; 107: 1239-44.

3. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. Arch Surg 1986 121: 1410-4.

4. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 1986; 152: 345-50.

5. Broders AC. Squamous cell epithelioma of the lip. A study of five hundred and thirty-seven cases. JAMA 1920; 74: 656-64.

6. Pindborg JJ, Reichart PA, Smith CJ, van der Waal I. Histological Typing of Cancer and Precancer of the Oral Mucosa. Second Edition ed. Berlin, Heidelberg, New York: Springer-Verlag; 1997.

7. Anneroth G, Batsakis JG, Luna MA. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. Scand J Dental Res 1987; 95: 229-49.

8. Bryne M, Koppang HS, Lilleng R, Stene T, Bang G, Dabelsteeen E. New malignancy grading is a better prognostic indicator than Broder's grading in oral squamous cell carcinomas. J Oral Pathol Med 1989; 18: 432-7.

9. Odell EW, Jani P, Sherriff M, Ahluwalia SM, Hibbert J, Levinson DA, Morgan PR. The prognostic value of individual histologic grading parameters in small lingual squamous cell carcinomas. Cancer 1994; 74: 789-94.

10. Hogmo A, Kuylenstierna R, Lindholm J, Munck-Wikland E. Predictive value of malignancy grading systems, DNA content, p53, and angiogenesis for stage I tongue carcinomas. J Clin Pathol 1999; 52: 35-40.

11. Lim SC, Zhang S, Ishii G, Endoh Y, Kodama K, Miyamoto S, Hayashi R, Ebihara S, Cho JS, Ochiai A. Predictive markers for late cervical metastasis in stage I and II invasive squamous cell carcinoma of the oral tongue. Clin Cancer Res 2004; 10: 166-72.

12. Okada Y, Mataga I, Katagiri M, Ishii K. An analysis of cervical lymph nodes metastasis in oral squamous cell carcinoma. Relationship between grade of histopathological malignancy and lymph node metastasis. Int J Oral Maxillofac Surg 2003; 32: 284-8.

13. Sawair FA, Irwin CR, Gordon DJ, Leonard AG, Stephenson M, Napier SS. Invasive front grading: reliability and usuefulness in the management of oral squamous cell carcinoma. JOral Pathol Med 2003; 32: 1-9.

14. Weijers M, Snow GB, Bezemer PD, Wal van der JE, Waal van der I. The clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients. J Oral Pathol Med 2002; 31: 11-5.

15. Weijers M, Snow GB, Bezemer DP, Wal van der JE, Waal van der I. The status of the deep surgical margins in tongue and floor of mouth squamous cell carcinoma and risk of local recurrence; an analysis of 68 patients. Int J Oral Maxillofac Surg 2004; 33: 146-9.

16. Sobin LH, Wittekind C. TNM Classification of Malignant Tumours, 6th Edition. International Union Against Cancer 2002; John Wiley & Sons, Inc.

17. Keski-Santti H, Atula T, Tikka J, Hollmen J, Makitie AA, Leivo I. Predictive value of histopathologic parameters in early squamous cell carcinoma of oral tongue. Oral Oncol 2007; 43: 1007-13.

18. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head Neck 1995; 17: 463-72.

19. Bryne M, Koppang HS, Lilleng R, Kjaerheim A. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol 1992; 166: 375-81.

20. Quinn CM, Wright NA. The clinical assessment of proliferation and growth in human tumours: evaluation of methods and applications as prognostic variables. J Pathol 1990; 160: 93-102.

21. Woolgar JA. T2 carcinoma of the tongue: the histopathologist's perspective. Br J Oral Maxillofac Surg 1999; 37: 187-93.

22. Amaral TMP, da Silva Freire AR, Carvalho AL, Lopes Pinto CA, Kowalski LP. Predictive factors of occult metastasis and prognosis of clinical stages I and II squamous cell carcinoma of the tongue and floor of the mouth. Oral Oncol 2004; 40: 780-6.

23. Kurokawa H, Zhang M, Matsumoto S, Yamashita Y, Tomoyose T, Tanaka T, Fukuyama H, Takahashi T. The high prognostic value of the histologic grade at the deep invasive front of tongue squamous cell carcinoma. J Oral Pathol Med 2005; 34: 329-33.

24. Poleksic S, Kalwaic HJ. Prognostic value of vascular invasion in squamous cell carcinoma of the head and neck. Plastic Reconstruc Surg 1978; 61: 234-40.

25. Shingaki S, Suzuki S, Nakajima T, Kawasaki T. Evaluation of histopathologic parameters in predicting cervical lymph node metastasis of oral and oropharyngeal carcinomas. Oral Surg Oral Med Oral Pathol 1988; 66: 683-8.

26. Brown B, Barnes L, Mazariegos J, Taylor F, Johnson J, Wagner RL. Prognostic factors in mobile tongue and floor of mouth carcinoma. Cancer 1989; 64: 1195-202.

27. Yuen PW, Lam KY, Chan AC, Wei WI, Lam LK. Clinicopathological analysis of local spread of carcinoma of the tongue. Am J Surg 1998; 175: 242-4.

28. Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN, Johnson JT. Perineural invasion of squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1998; 124: 637-40.

29. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2003; 32: 30-4.

30. McMahon J, O'Brien CJ, Pathak I, Hamil R, McNeil E, Hammersley N, Gardiner S, Junor E. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg 2003; 41: 224-31.

Chapter 6

Patients with oral cancer developing from pre-existing oral leukoplakia: do they do better than those with de novo oral cancer?

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Abstract

Background: It has been suggested that patients with squamous cell carcinomas derived from oral leukoplakia have a better prognosis than patients with carcinomas that are not associated with oral leukoplakia.

Aim: To study the mortality rate of 19 patients with a squamous cell carcinoma derived from pre-existing oral leukoplakia.

Method: The mortality rate of 19 patients with a proven oral squamous cell carcinoma derived from a pre-existing oral leukoplakia was compared with that of a similar size group of patients with oral carcinoma without a pre-existing oral leukoplakia, being matched for gender, age, smoking habits, use of alcohol, oral subsite and histopathologic grade. Treatment in all patients was primarily by surgical excision. The mortality rates up to 5 years have been computed according to the Kaplan-Meier method.

Result: No significant difference of the mortality rates up to 5 years of follow-up was observed between the two groups of patients.

Conclusion: Patients with oral cancer developing from pre-existing oral leukoplakia do not do better than those with *de novo* oral cancer.

Introduction

It has been stated that squamous cell carcinomas associated with or derived from oral leukoplakia appear to be smaller, to be histologically more mature, to be only superficially invasive and, therefore, provide a better prognosis than similar carcinomas that are not associated with oral leukoplakia (1).
The present study was undertaken to compare the 5-year mortality rates of patients with an oral squamous cell carcinoma arisen from pre-existing oral leukoplakia with a matched control group of patients with *de novo* oral squamous cell carcinoma.

Patients and methods

Nineteen patients with an oral squamous cell carcinoma that had developed from pre-existing oral leukoplakia were matched with a group of 19 patients with a primary oral squamous cell carcinoma drawn from the oncology data base of the Department of Oral and Maxillofacial Surgery of the Vrije Universiteit University Medical Center, Amsterdam, the Netherlands. Matching was performed with regard to gender, age, smoking habits, use of alcohol, oral subsite, TNM stage and histopathologic grade.
The group of patients with pre-existing oral leukoplakia has been published in detail elsewhere (2). The data of both patients groups are summarized in Table 1. All patients of both groups were initially treated by surgery.
All but one carcinoma developed inside the region of the leukoplakia. The malignant transformation occurred in a mean period of 32 months (range 6–201 months). The mortality rates up to 5 years for both groups of patients have been computed according to the Kaplan–Meier method (3), allowing for patients lost to followup.
Mortality was defined in two ways: from all causes or from oral squamous cell carcinoma. The patient groups were compared with the log rank test. The results were considered statistically significant if the value of $P < 0.05$.

Table 1 Matching data of 19 patients with a squamous cell carcinoma arisen in a pre-existing oral leukoplakia and 19 patients with de novo carcinoma

	Carcinoma arising from Pre-excisting oral leukoplakia	Carcinoma arising de novo
Number of patients	19	19
Gender		
Male	3	3
Female	16	16
Mean age (years)	71.6	71.5
Smoking habits		
Non-smokers	12	12
Smokers	7	7
Alcohol use		
Non-users	10	11
Users	9	8
Oral subsite		
Tongue (mobile part)	9	11
Floor of mouth	3	3
Cheek	2	2
Lower jaw	2	2
Multifocal	2	1
Unknown	1	-
TNM Classification		
T is	2	1
T1	7	6
T2	8	9
T3	1	3
T4	1	-
All patients were clinically staged as N0 M0		
Histopathologic grade		
Carcinoma in situ	2	1
Well-differentiated	8	11
Moderately/poorly differentiated	8	7
Verrucous carcinoma	1	-

Results

In Table 2, the follow-up of the patient groups, including the 5-year mortality according to the Kaplan–Meier method, have been shown for both definitions of mortality. No statistically significant differences between the groups were found (log rank test; P = 0.38 and 1.00 respectively).

Table 2 Five-year follow-up data of 19 patients with a squamous cell carcinoma arising in a pre-existing oral leukoplakia and 19 patients with de novo carcinoma

	Carcinoma arising from Pre-excisting oral leukoplakia	Carcinoma arising de novo
Number of patients	19	19
Lost to follow-up	1a	3b
Dead of other causes	3c	6d
Dead of disease	3	3
Five-year mortality rate (%), all causes	32	53
Five-year mortality rate (%), carcinoma	16	20

a After 1 year.
b After 1 and 2 years (two patients), respectively.
c After 1, 2 and 3 years respectively.
d After 2 years (four patients), 3 years and 4 years respectively.
Log rank: p = 0.38 (all causes) and p = 1.00 (carcinoma).

Discussion

The disproportional gender ratio in the pre-existing oral leukoplakia group was the reason to match for gender.
The same applies for the reason to match for the oral subsite, the prevalence of tongue carcinomas in the preexisting oral leukoplakia group being rather high, e.g. in comparison with the prevalence of cancer of the floor of the mouth.
In patients being followed for possible malignant transformation of their oral leukoplakia one would expect to encounter only T1 carcinomas. Apparently, this has not been the case. Just over half of the patients had T2 or even larger carcinomas. The large size of the carcinomas can probably be explained by the follow-up intervals of the leukoplakia patients, that varied from 3 to 12 months, while some of these patients were even lost

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to follow-up until the time that they were readmitted because of cancer development (2). In a recent Cochrane review, it has been concluded that treatment of oral leukoplakia does not necessarily preclude future development of a squamous cell carcinoma (4). Therefore, close follow-up of both treated and untreated patients may be warranted, although the benefit of such follow-up visits has still not been proven yet. There are no universally accepted guidelines in the literature about the period of the intervals, e.g. 6 months, of such followup visits, nor about the length.

In the pre-existing leukoplakia group, a relatively large proportion of non-smokers and non-users of alcohol was observed. This finding too can be explained by the source of the study group, i.e. the patients who had their cancer developing from a leukoplakia. It is generally accepted that malignant transformation of oral leukoplakia is more likely to occur in smokers than in non-smokers. Less is known about the possible role of alcohol in the prediction of malignant transformation of oral leukoplakia.

In view of the rather limited number of patients, the present data should be looked upon carefully. Nevertheless, the figures do no support the hypothesis that patients with oral carcinomas associated with or derived from oral leukoplakia have a better prognosis than those with an oral carcinomas without concomitant or preceding oral leukoplakia. Although mortality from all causes seems lower, this is far from significant ($p = 0.38$).

In our oral leukoplakia-derived cancer patients another four patients died from their disease after 7,12, 18 and 19 years respectively. These long-term follow-up data could not be compared with the findings of the de novo group, as the maximum follow-up period of that group lasted 10 years only. It has been suggested that patients with carcinoma of the tongue with concomitant oral leukoplakia show a five times greater incidence of the development of subsequent multiple carcinomas of the oral cavity and pharynx than patients without oral leukoplakia, which likely may result in a poorer prognosis (5).

References

1. Bouquot JE, Weiland LH, Kurland LT. Leukoplakia andcarcinoma in situ synchronously associated with invasive oral/oropharyngeal carcinoma in Rochester, Min., 1935–1984. Oral Surg Oral Med Oral Pathol 1988; 65: 199–207.

2. Schepman KP, Meij van der EH, Smeele LE, Waal vander I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakie from The Netherlands. Oral Oncol 1998; 34: 270–5.

3. Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.

4. Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A. Interventions for treating oral leukoplakia (review). The Cochrane Library 2007; 1: 1–24.

5. Shibuya H, Amagasa T, Seto KI, Ishibashi K, Horiuchi JI. Leukoplakia-associated multiple carcinomas in patients with tongue carcinoma. Cancer 1986; 57:843–6.

Chapter 7

Oral Cancer trends in a single Head-and-neck cancer center in the Netherlands; decline in T-stage at the time of admission

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Abstract

Objectives: In this study we evaluated the possible epidemiologic changes of oral cancer patients in the Netherlands between the years 1980-1984 and 2000-2004. We specifically studied the differences in male-female ratio, age, TNM-stage, site distribution, and alcohol and tobacco use.

Materials and Methods: Patients from the VU University Medical Center with an oral squamous cell carcinoma of the oral cavity registered in 1980-1984 (n=200) Group 1,were compared to patients registered in 2000-2004 (n=184) Group 2. Trends in prevalence, site distribution, TNM-stage, alcohol and tobacco use, age and gender were studied.

Results: The male-female ratio has decreased from 1.8 to 1.2. There were no differences in age between the two groups of patients. The site distribution was similar in both groups. The most commonly involved sites were the tongue and the floor of mouth.
In group 2 more patients were diagnosed with a T1 tumor. There were no differences in tobacco use between the two different groups. There were much more light drinkers (0-2 drinks per day) in group 2 than in group 1, whereas there were more heavy drinkers (>4 per day) in group 1 than in group 2 (p=<0.001). This was observed in both male and female patients.

Conclusion: In our study there were no significant differences between the patients registered in the years 1980-1984 and 2000-2004 regarding the mean age of the patients, site distribution and smoking habits. The male female ratio has decreased. In the recent group more patients were staged T1N0 and there was a strong decrease of the patients who were heavy drinkers.

Introduction

Squamous cell carcinoma makes up approximately 90% of oral cancers, the remaining 10% consisting of malignant salivary gland tumors of the accessory glands, melanoma, sarcomas of the soft tissues and the jaw bones, malignant odontogenic tumors, non-Hodgkin lymphomas and metastases from primary tumors located elsewhere in the body.
The main etiologic factors of oral squamous cell carcinoma (OSCC) are tobacco and alcohol use (1-3). Human papilloma virus, particular type 16, may play an etiologic role in a small subset of patients (4).
In the past decade several studies have been published that showed an increase in the incidence of OSCC, a tendency to occur more often in the age group below the age of 40 years.
In the present study the possible epidemiologic changes of oral cancer patients treated at the VU University Medical Center, Amsterdam, have been examined comparing the periods 1980-1984 and 2000-2004. We specifically studied the possible differences in the male-female ratio, age, subsite distribution, TNM-stage, and alcohol and tobacco use.

Material and Methods

Patients were drawn from the oral cancer database of the VU University Medical Center, Amsterdam, the Netherlands. In this study only patients with a squamous cell carcinoma of the oral cavity were studied (ICD 10 141, 143-145).
The data of patients registered in the period 1980-1984 were compared to those of patients registered in the period 2000-2004. For the statistical analysis chi-square tests were used and an independent sample t-test for the difference between the groups regarding age. A p value < 0,05 was considered as statistical significant.

Results

In the period 1980-1984 (group 1) a total number of 200 patients with an oral squamous cell carcinoma was registered, while that number was 184 in the period 2000-2004 (group 2).
Gender and age are summarized in table 1. The ICD codes and specified

sites are depicted in table 2. The clinical T and N stages are depicted in table 3, while the data about smoking habits and the use of alcohol are summarized in tables 4 and 5, respectively.

Table 1: Demographic data

	Group 1 (1980-1984) N=200	Group 2 (2000-2004) N=184	P value
Male	129 (64.5%)	102 (55.4%)	0.070
Female	71 (35.5%)	82 (44.6%)	
Mean age (SD)	64 (12.97)	63 (12.65)	0.238
Number of patients below 40 years	10	8	0.763

Note: no statistically significant differences were observed between the two periods

Table 2: Localisation of oral squamous cell carcinomas

Localisation	Group 1 (1980-1984)	Group 2 (2000-2004)
Lower Lip (C00.1, 2, 4, 5, 8, 9)	14	17
Tongue (C02.0, 1, 2, 3, 8, 9)	57	58
Gingiva maxilla (C03.0)	10	4
Gingiva mandible (CO3.1)	40	26
Floor of Mouth (C04.0, 1, 8, 9)	62	51
Cheek (C06.0)	7	9
Palate C05.0, 1, 9	5	2
Multifocal C06.8	2	2
Other	3	15
Total	200	184

Note: no statistically significant differences were observed between the two periods.

The male-female ratio in group 1 was 1.8: 1 and this ratio was 1.2: 1 in group 2. There were no significant differences in age between the two groups of patients. No increase of patients under the age of 40 years was observed. The distribution of the oral subsite of the tumours as indicated in (table 2) showed no change either. The most common subsites were the lateral borders of the tongue and the floor of mouth.
The T-stage is visualized in table 3. There are more patients in group 2 with T1 stage (p 0.015) compared to the patients from the first group. The N-stage is also shown in table 3. There are significantly more patients in the group 2 with a lower N-stage, (p<0.001) than in the first group.
There were no statistically significant differences in tobacco use in both men and women between the two periods. With regard to the use of alcohol a statistical significant difference was found: there were more light drinkers in the category 0-2 drinks per day in group 2 than in group 1, whereas there were more heavy drinkers (>4 per day) in group 1 than in group 2 (p=<0.001). This was found in both male and female patients.

Table 3: T-stage, N-stage and T1N0

T-stage	Group 1 (1980-1985) n=200	Group 2 (2000-2004) n=184
T1	48	69*
T2	84	60
T3	48	32
T4	20	23
N-stage		
N0	124	148**
N1	55	22
N2	15	14
N3	6	-
T1N0	45	66***

* There is a significant higher number of patients with T1 in group 2 (p=0.015)
**There is a significant increase in patients with N0-stage in group 2 (p<0.001)
***There is a significant increase in patients with T1N0-stage in group 2 (p=0.032)

Table 4: Smoking habits

Smoking habits	Group 1 (1980-1985)			Group 2 (2000-2004)		
	Total	Men	Women	Total	Men	Women
Non-smoker	58	22	36	62	27	35
<10 sig/day	10	7	3	5	3	2
10-20 sig/day	38	33	5	22	17	5
>20 sig/day	82	61	21	67	38	29
Not registered	12	-	-	28	-	-
Total	188	123	65	156	85	71

Note: no statistically significant differences in smoking habits among men (p=0.120) and women (p=0.745) in the two periods.

Table 5: Alcohol use

Alcohol use	Group 1 (1980-1985)			Group 2 (2000-2004)		
	Total	Men	Women	Total	Men	Women
None	44	18	26	23	9	14
0-2 per day	32	16	16	60	31	29
2-4 per day	49	41	8	37	22	15
>4 per day	59	45	14	27	19	8
Not registered	16	9	7	37	21	16
Total	184	120	64	147	81	66

Note: there were statistically significant more light drinkers (0-2 per day) in the second period, both in men (p=0.001) and women (p=0.011).

Discussion

In the majority of the literature an increase of patients with oral cancer was observed in the past decades.
Warnakulsaya et al. stated that in the last two decades there was an increase of both oral and oropharyngeal cancer in Western Europe (5). Karim-Kos et al. found an increase of smoking related cancers in whole Europe (6). Curado et al. comparing data from 1998 and 2002 found an increase in incidence in oral cancer for both men and women for North and East Europe and a stable incidence in the West of Europe (7). However, it seems somewhat questionable to compare data obtained from two

periods with an interval of just four years.
On the other hand, a decrease in the age-standardized incidence of oral squamous cell carcinoma in the last three decades in the U.S. has been reported (8). In a recent European study it was noted that oral cancer mortality has started to decline in generations born after the 1950's (9).
Since there was no formal cancer registry in the Netherlands yet in the first period (1980-1984) no reliable information is available about a possible increase of oral cancer in the Netherlands when comparing the period 1980-1984 and the period 2000-2004. Braakhuis et al. reported a stable incidence for oral cancer in men and an increasing incidence in women over the years 1989-2006 (10).
The male-female ratio decreased in the present study. This is also seen in other studies (6). Apparently, this decrease was not related to a decrease of smoking habits among men nor an increase of smoking in woman as will be discussed later.
In our study no change in the mean age of the patients was observed. The number of patients below 40 years of age remained stable. This is in accordance with the study by Muller et al. who observed a more than fourfold increase of patients below 40 years of age in the period between 1974 and the late 1980´s and then remaining stable thereafter until 2006 (9). In a few studies, amongst others from Scotland and Ireland, an increasing incidence of oral cancer in young patients has been reported (12,13). No convincing explanation could be provided for that finding (14).
No differences between our two groups of patients were seen with regard to site distribution. The most common sites are the lateral borders of the tongue and the floor of mouth. This is in accordance with the literature (15-18).
In this study a clear difference between the two groups concerning T1- and N0-stages was seen. Remarkably, there were more patients diagnosed with T1 tumors in the 2000-2004 period. This suggests that patients with oral cancer are diagnosed in an earlier stage. Perhaps, this is caused by improved education of the public or increased awareness among dental and medical practitioners. In a study from an other head and neck cancer center in the Netherlands an increase in the percentage of patients with T4 oral cancers was observed, being 22,7% in the 1985-1989 period and 32,9% in the 1995-1998 period (19), while in the present study this percentage has only slightly increased in the two studied periods (10,0% and 12,5% respectively, being statistically not significantly different).

In the study by Hoffman et al. the distribution of stages remained stable when comparing the years 1985-1989 and 1990-1994 in the US (20). However, in that study no distinction was made between cancer of the oral cavity and other head and neck cancers.

Interestingly, in the present study in 2000-2004 more patients were classified with N0 stage of the neck. In the early 90´s the ultrasound guided fine needle aspiration was introduced for the staging process of the neck, which would result in a lower number of N0 cases. Most likely the increase of N0 patients in our group 2 (2000-2004) is related to the increased number of patients presenting with a lower T-stage at admission.

In the Netherlands there is a clear decrease of the number of smokers after 1980. In 1980 43% of the population was smoking; in 2004 that number was 28%. However, we have not noticed this decrease in our patient groups. In male as well as female patients no differences in smoking habits between the two groups were observed. In our study no statistically significant difference in smoking habits in women between the two periods was observed.

In the present study a significant decrease in the number of heavy drinkers between the two groups was observed; the percentages dropped from 32% in the 1980-1984 period to 18% in the 2000-2004 period. In spite of less alcohol consumption and, in men, decreased smoking habits, one would expect to observe a decrease in the incidence of oral cancer, which is apparently not the case. No proper explanation can be provided for this observation (2,3).

References

1. Bray I, Brennan P, Boffeta P. Projections of alcohol-and tobacco-related cancer mortality in Central Europe. Head Neck 2007;27:779-792

2. Gillison ML. Current Topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck 2007;29:779–792

3. La Vecchia C, Tavani A. Epidemiology and prevention of oral cancer. Oral Oncology 1997;33:302-312

4. Syrjanen S, Lodi G, van Bultzingslowen I, et al. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Dis 2011;17:58-72.

5. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncology 2009;45:309–316.

6. Karim-Kos HE, de Vries E, Lemmens V, Siesling S, Coebergh J.W. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. European Journal of Cancer 2008;44: 1345-1389

7. Curado MP , Hashibe M. Recent changes in the epidemiology of head and neck cancer. Current Opinion in Oncology 2009;1:194–200.

8. Charturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papilloma virus-related and –unrelated oral squamous cell carcinomas int the United States. J Clin Oncol 2008;2:60-6.

9. Bonifazi M, Malvezzi M, Bertuccio P, et al. Age period-cohort analysis of oral cancer mortality in Europe: The end of an epidemic? Oral Oncol 2011;47:400-407.

10. Braakhuis BJ, Visser O, Leemans R. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral oncology 2009;45:e85-9

11. Müller S, Pan Y, Ruosha L, Chi AC. Changing Trends in Oral Squamous Cell Carcinoma with Particular Reference to Young Patients: 1971-2006. The Emory University Experience. Head and Neck Pathol 2008;2:60-66

12. Mackenzie J, Ah-See K, Thakker N, Sloan P, Maran AG, Birch J, Macfarlane GJ. Increasing incedence of oral cancer amongst young persons: what is the etiology. Oral Oncol 2000;36:387-389.

13. O'Regan EM, Timon C, Sheils O, codd M, O'Leary JJ, Toner M. Squamous cell carcinoma of the head and neck in young Irish adults. Br J Oral Maxillofac Surg 2006;44:203-206.

14. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasukariya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncol 2004;40:304-313.

15. Gorsky M, Epstein JB, Oakley C, Le ND, Hay J, Stevenson-Moore P. Carcinoma of the tongue: a case series analysis of clinical presentation, risk factors, staging, and outcome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:546-52.

16. Lam L, Logan RM, Luke C. Epidemiological analysis of tongue cancer in South Australia for the 24-year period, 1977–2001. Australian Dental Journal 2006;51:16-22.

17. Moore SR, Johnson NW, Pierce AM, Wilson DF. The epidemiology of tongue cancer: a view of global incidence. Oral Dis 2000;6:75–84.

18. Rusthoven K, Ballonoff A, Raben D, Chen C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma.Cancer 2008;112:345-351.

19. Brouha XDR, Tromp DM, De Leeuw JRJ, Koole R, Slootweg PJ, Hordijk GJ. Stijgende incidentie van invasieve (T4)-hoofd-halscarcinomen in het Universitair Medisch Centrum Utrecht, 1980-1998. Nederl Tijdschr Geneeskd 2002;146:1131-1135.

20. Hoffman HT, Karnell L.H. The National Cancer Data Base Report on Cancer of the Head and Neck. Arch Otolaryngol Head Neck Surg. 1998;124:951-962.

Chapter 8

Summary and conclusions

Summary and conclusions

The present study is mainly focussed on the clinical relevance of a number of histopathological aspects of small (T1,T2) squamous cell carcinomas of the tongue and floor of mouth. In addition, some epidemiological aspects have been studied. After the introductory **chapter 1**, some aspects of the etiology, diagnosis, histopathology and staging of oral squamous cell carcinomas have been discussed in **chapter 2**. In **Chapter 3,** the clinical relevance of the presence of epithelial dysplasia in the surgical mucosal margins of tongue and floor of mouth squamous cell carcinomas with regard to local recurrence has been reported. A total number of 37 patients who have been surgically treated for a primary squamous cell carcinoma of the tongue and the floor of the mouth have been included. The follow-up was five years. Local recurrence occurred in two out of 30 patients in whom no epithelial dysplasia was present, while 5 out of 7 patients with epithelial dysplasia developed a local recurrence, the difference between these two groups being statistically significant (Fisher exact test; $p< 0.01$). Indeed, presence of epithelial dysplasia in the surgical mucosal margin has predictive value with regard to the development of local recurrence. Therefore, we recommend that the presence of dysplasia in the mucosal margin is mentioned in the histopathological report and advise the clinician in case of dysplasia (mild as well as moderate and severe) within the margins to immediately perform a reexcision of the tumor site because of the high risk of local recurrence.
Unfortunately, the study on the role of DNA-ploidy measurement of J. Sudbö (reference 12 chapter 3) has been withdrawn.
In **chapter 4**, the clinical relevance of tumor free deep surgical margins in oral carcinoma was studied retrospectively. A total of 68 patients was included. All patients underwent surgical treatment of a squamous cell carcinoma of the tongue or floor of mouth. The follow-up was five years. Local recurrence occurred in two out of 30 patients with a tumor free deep surgical margin (no tumor within 0.5cm) and in 3 out of 38 patients with a close (tumor less than 0.5 cm) deep surgical margin This difference was not statistically significant. Therefore, no additional treatment in case of a close deep surgical margin (<0.5) seems to be required. However, margin status has proved to be of prognostic value in overall survival. A recent study of Nason et al, (1) showed a statistically significant decreased 5-year survival rate in patients with positive margins as well as close (<3mm) margins. These findings are in concordance with Binahmed et al,

(2) who found that involved surgival margins increased the risk of death at 5 years by 90%. In summary, we recommend additional treatment in case of involved or close (<3mm) deep surgical margins to improve the survival rate of the patient.
In **chapter 5** the results of a retrospective study on the possible value of the so-called histopathological malignancy grading system have been reported. For this purpose, the classical Broders' grading system and the malignancy grading system have been compared with regard to various outcome measures such as regional metastasis, local recurrence and 5-year survival in a number of 128 previously untreated patients with a T1 or T2 squamous cell carcinoma of the tongue and the floor of the mouth. The results show that neither histopathological grading system has a strong predictive value and that none is superior to the other. Our advise to pathologists, however, is to use the malignancy grading system (MGS) of Anneroth and Bryne and to score the different items at the tumor front (invasive front grading). This because of the accuracy of the system and the clear scoring of the different items. What we did find in the study in chapter 5 was a tendency (not statistically significant) that perineural spread was associated with poor survival and that tumor growth in vessels was associated with increased risk of regional metastasis. Perineural spread is widely accepted as a prognostic factor of tumor aggressiveness. However, the specific mechanisms are not clear yet and further investigations are needed to develop therapeutic agents (3). Perineural spread and tumor growth in vessels are, indeed, important items to be mentioned in the pathologist's report and, when present, additional treatment should be considered.
In the past decades numerous molecular and immunohistochemical markers have been examined for their possible predictive value of tumor behaviour of oral squamous cell carcinoma. No final conclusions can be drawn yet, with the possible exception of HPV type 16 positive tumors, particularly in cancer of the oropharynx, that seem to have a better prognosis and also show a better response to radiotherapy.
In **chapter 6**, the mortality rate of 19 patients with a proven oral squamous cell carcinoma derived from a pre-existing oral leukoplakia was compared with that of a similar size group of patients with oral carcinoma without a pre-existing oral leukoplakia, being matched for gender, age, smoking habits, use of alcohol, oral subsite and histopathologic grade. Treatment in all patients consisted primarily of surgical excision. No significant

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difference between the mortality rates up to five years of follow-up was observed between the two groups of patients. Apparently, patients with oral cancer developing from pre-existing oral leukoplakia do not do better than those with de novo oral cancer as sometimes has been suggested in the literature. Untill now, no treatment regimen has proven to truly prevent malignant transformation of oral leukoplakia (4). Nevertheless, the general advice is to treat oral leukoplakia, if feasible, and to have the patient followed at intervals of no more than 4-6 months, lifelong.

In **chapter 7,** the possible epidemiologic changes of oral cancer patients in the Netherlands between the years 1980-1984 and 2000-2004 are evaluated. The male-female ratio, age, TNM-stage, site distribution, and alcohol and tobacco use were studied. Patients from the VU University Medical Center (formerly known as Free University Medical Centre) with squamous cell carcinoma of the oral cavity registered in 1980-1984 (n=200; group 1),were compared to patients registered in 2000-2004 (n=184; group 2). Trends in prevalence, site distribution, TNM-stage, alcohol and tobacco use, age and gender were studied. The male/female ratio in group 2 has decreased from 1.8 to 1.2. There were no differences in age between the two groups of patients. The site distribution was similar in both groups. The most commonly involved sites in both groups were the tongue and the floor of mouth. In group 2 more patients were diagnosed with a T1 tumor. There were no differences in tobacco use between the two different groups. There were much more light drinkers (0-2 drinks per day) in group 2 than in group 1, whereas there were more heavy drinkers (>4 per day) in group 1 than in group 2 (p=<0.001). This was observed in both male and female patients.

This study certainly leaves room for discussion. There are several methodological flaws. The studied patients were only patients treated at the Free University Medical Center in Amsterdam and this group of patients might not be representative in various aspects- such as ethnic background, age and gender- for the total population of Amsterdam or even The Netherlands. Even in a small country as The Netherlands, the demographic profile varies per geographic region. Furthermore, there might have been differences in the referral pattern in the two studied periods in Amsterdam where another head-and-neck cancer center is located. On the other hand, it is unlikely that such event may explain the observed differences with regard to the various parameters that have been studied. Nevertheless, the results of the present study should be

looked at with some reservation.

We can conclude that, inspite of ongoing developments in different fields of diagnosis and treatment, i.e. imaging, surgical techniques, radiotherapy, and chemotherapy, the overall survival rate of patients with oral cancer has not improved over the last decades. Even in early (T1,T2) carcinomas there is a serious number of patients who develop locoregional metastasis, suffer from recurrent disease or die of their disease. For prevention, creating awareness among patients as well as among primary health care workers, i.e. dentists and general medical practitioners, is of great importance. Especially creating awareness of the main risk factors like alcohol consumption and smoking can be of great importance. Primary health care workers can play a great role, indeed, in the cessation of tobacco and alcohol habits.

References

1. Nason RW, Binahmed A, Pathak KA, Abdoh AA, Sbndor GKB. What is the adequate margin of surgical resection in oral cancer? Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2009; 107(5):625-629.

2. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncology 2007; 43(8):780-784.

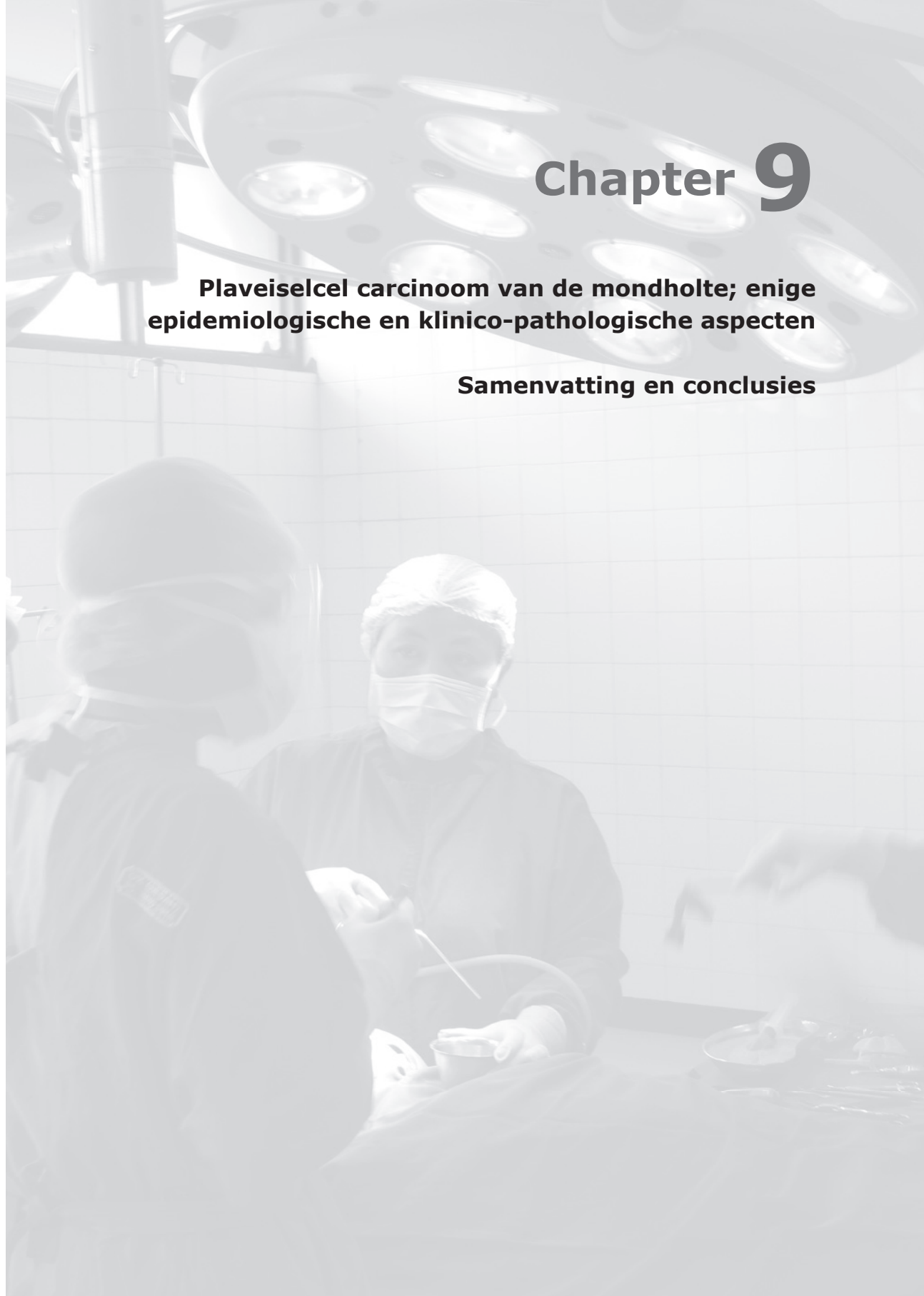
3. Binmadi NO, Basile JR. Perineural invasion in oral squamous cell carcinoma: A discussion of significance and review of the literature. Oral Oncology 2011; 47(11):1005-1010.

4. Lodi G, Sardella A, Bez C, Demarosi F, Carassi A. Interventions for treating oral leukoplakia (Review) 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chapter 9

Plaveiselcel carcinoom van de mondholte; enige epidemiologische en klinico-pathologische aspecten

Samenvatting en conclusies



Samenvatting en conclusies

Deze studie is hoofdzakelijk gericht op de klinische relevantie van een aantal histopathologische aspecten van kleine (T1,T2) plaveiselcelcarcinomen van de tong en mondbodem. Tevens werden enkele epidemiologische aspecten bestudeerd. Na het introductie **hoofdstuk 1**, zijn enige aspecten van de etiologie, diagnose, histopathologie en stagering van het plaveiselcelcarcinoom van de mondholte belicht in **hoofdstuk 2**. In **hoofdstuk 3** is de klinische relevantie van de aanwezigheid van epitheeldysplasie in de chirurgische slijmvliesresectieranden van tong- en mondbodem plaveiselcelcarcinomen in relatie tot het eventueel optreden van lokaal recidief besproken. In het totaal zijn 37 patiënten geïncludeerd die chirurgisch behandeld zijn voor een primair plaveiselcelcarcinoom van de tong of de mondbodem. De follow-up tijd was 5 jaar. Lokaal recidief trad op in 2 van de 30 patiënten bij wie geen dysplasie in de resectieranden gezien was, terwijl dit bij 5 van de 7 patiënten optrad met epitheeldysplasie in de resectieranden. Het verschil tussen deze twee groepen was statistisch significant (Fisher exact test: $p<0.01$). Hiermee is aangetoond dat epitheeldysplasie in de chirurgische slijmvliesranden voorspellende waarde heeft voor het ontstaan van een lokaal recidief. Daarom adviseren wij om de aanwezigheid van dysplasie in de chirurgische slijmvliesranden te vermelden in het histopathologie verslag en tevens adviseren wij de chirurg om in het geval van dysplasie (zowel mild, matig als ernstig) direct een reëxcisie uit te voeren vanwege het grote risico op een lokaal recidief.

In **hoofdstuk 4** is retrospectief de klinische relevantie van tumorvrije diepe chirurgische resectieranden in mondholtecarcinomen bestudeerd. In totaal zijn 68 patiënten onderzocht. Alle patiënten hadden een chirurgische behandeling ondergaan voor een plaveiselcelcarcinoom van de tong of de mondbodem. De follow-up tijd was 5 jaar. Lokaal recidief trad op in 2 van de 30 patiënten met een tumorvrije resectierand (geen tumor binnen 0.5cm van de resectierand) en in 3 van de 38 patiënten met een krappe tumorvrije resectierand (tumor minder dan 0.5cm van de resectierand). Dit verschil was statistisch niet significant.

In geval van een krappe diepe chirurgische resectierand (<0.5cm) is aanvullende behandeling niet altijd noodzakelijk. Niettemin, de status van de resectieranden heeft bewezen prognostische waarde wat betreft de overleving van de patiënt. Een recente studie van Nason (1), liet een significant verlaagde 5-jaars overleving zien bij zowel patiënten met

een positieve resectierand, als bij patiënten met een krappe (<3mm) resectierand. Deze bevindingen komen overeen met de studie van Binhamed (2). Deze studie toonde aan dat positieve resectieranden het risico op overlijden binnen 5 jaar met 90% deed toenemen. Samenvattend adviseren wij aanvullende behandeling in het geval van positieve of krappe (<3mm) resectieranden om de overlevingskansen van de patiënt te verbeteren.

In **hoofdstuk 5** zijn de resultaten van een retrospectieve studie naar de mogelijke waarde van het maligniteits graderingssysteem gepresenteerd. De voorspellende waarden van het klassieke Broders graderingssysteem en het maligniteits graderingssysteem zijn beoordeeld op verschillende parameters, zoals regionale metastasen, lokaal recidief en 5 jaars-overleving. Hiervoor zijn 128 niet eerder behandelde patiënten met een T1- of T2 plaveiselcelcarcinoom van de tong of de mondholte onderzocht. De resultaten tonen aan dat geen van de histopathologische graderingssystemen een sterk voorspellende waarde heeft en dat het ene systeem niet superieur is aan het andere. Toch is ons advies aan pathologen om het maligniteits graderingssysteem (MGS) van Anneroth en Bryne te gebruiken en de verschillende items in het tumorfront te scoren (invasive front grading). Dit vanwege de accuratesse van het systeem en het duidelijke scoren van de verschillende onderdelen. In hoofdstuk 5 werd er wel een tendens (niet statistisch significant) gevonden dat perineurale groei geassocieerd is met een slechte overleving en dat tumor groei in vaten geassocieerd is met een verhoogd risico op regionale metastasen. Perineurale groei is algemeen geaccepteerd als een prognostische factor voor tumor agressiviteit. De specifieke mechanismen zijn nog niet geheel duidelijk en nader onderzoek is nodig om therapeutische middelen te ontwikkelen (3). Perineurale groei en tumor groei in vaten zijn inderdaad belangrijke items om te vermelden in het verslag van de patholoog en indien aanwezig zal aanvullende behandeling overwogen moeten worden. In de afgelopen decennia zijn vele moleculaire immunohistochemische markers onderzocht op hun eventuele voorspellende waarde van de agressiviteit van het orale plaveiselcelcarcinoom. Er kunnen nog geen eindconclusies getrokken, worden maar het lijkt erop dat tumoren die HPV type-16 positief zijn een betere prognose hebben en ook een betere reactie geven op radiotherapie.

In **hoofdstuk 6** is het sterftecijfer van 19 patiënten met een plaveiselcelcarcinoom ontstaan vanuit leukoplakie vergeleken met

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dat van een eveneens uit 19 patiënten bestaande groep met een plaveiselcelcarcinoom niet ontstaan vanuit leukoplakie. De groepen zijn "gematched" voor geslacht, leeftijd, rookgewoonten, alcoholgebruik, locatie in de mond en histopathologische gradering. Alle patiënten zijn primair chirurgisch behandeld. De sterftecijfers tot 5 jaar na behandeling zijn berekend volgens de Kaplan-Meier methode. Er is geen significant verschil gevonden tussen de twee groepen patiënten wat betreft de sterftecijfers. Hieruit blijkt dat patiënten met een mondholtecarcinoom ontstaan vanuit leukoplakie geen betere overleving hebben dan patiënten met een mondholtecarcinoom dat niet ontstaan is vanuit leukoplakie.
Tot nu toe heeft geen enkele behandeling echt bewezen dat het maligne transformatie van een leukoplakie kan voorkomen (4). Ondanks dat is het algemene advies om een leukoplakie van de mondholte, indien mogelijk, te behandelen en de patiënt levenslang te controleren met een interval van niet meer dan 4-6 maanden.
In **hoofdstuk 7** zijn de mogelijke epidemiologische veranderingen van patiënten met een mondholtecarcinoom in Nederland in de jaren 1980-1984 en 2000-2004 onderzocht. Er werd gekeken naar de verschillen in man-vrouw verhouding, leeftijd, TNM-stadium, lokalisatie en alcohol- en tabakgebruik. Patiënten van het Vrije Universiteit Medisch Centrum met een plaveiselcelcarcinoom van de mondholte, geregistreerd in 1980-1984 (n=200; groep 1), zijn vergeleken met patiënten geregistreerd in 2000-2004 (n=184; groep 2). De man-vrouw verhouding in de tweede groep nam af van 1.8 tot 1.2. Er waren geen verschillen in leeftijd tussen de twee patiëntengroepen. De verdeling van de lokalisaties was gelijk in beide groepen. De meest voorkomende lokalisaties in beide groepen waren de tong en de mondbodem. In de tweede groep zijn meer patiënten gediagnosticeerd met een T1 tumor. Het is onbekend of deze 'eerdere' diagnose heeft geresulteerd in een betere overleving van de patiënten in deze groep. Er waren geen verschillen in tabakgebruik tussen de twee groepen. Wel werden er verschillen in alcoholgebruik waargenomen. Er waren meer lichte drinkers (0-2 consumpties per dag) in de tweede groep dan in de eerste, terwijl er meer zware drinkers (>4 per dag) in de eerste groep patiënten waren. Dit gold voor zowel mannen als vrouwen.
Deze studie laat zeker ruimte voor discussie. Er zijn namelijk enige methodologische gebreken. De bestudeerde patiënten groep bestond alleen uit patiënten die behandeld waren in het Vrije Universiteit Medisch Centrum in Amsterdam. Deze groep is wellicht niet representatief in

verscheidene opzichten- zoals etnische achtergrond, leeftijd en geslacht- voor de totale Amsterdamse populatie of zelfs de Nederlandse populatie. Zelfs in een klein land als Nederland varieert het demografische profiel per provincie. Tevens is het mogelijk dat er verschillen zijn opgetreden in het patroon van verwijzen in Amsterdam, waar nog een ander hoofd-hals kanker-centrum is gelokaliseerd, tussen de twee bestudeerde periodes. Aan de andere kant is het onwaarschijnlijk dat dit gegeven de gevonden verschillen tussen de verschillende parameters kan verklaren. Desalniettemin moeten de resultaten van deze studie met enige terughoudendheid worden bekeken.
Concluderend kan worden gesteld, dat ondanks voortschrijdende ontwikkelingen op verschillende gebieden zoals beeldvorming, chirurgische en radiotherapeutische technieken en chemotherapie, de gemiddelde overlevingskans van patiënten met mondholtecarcinomen de laatste decennia niet duidelijk is verbeterd. Zelfs in een vroeg stadium (T1,T2) is er een groot aantal patiënten die lokale metastasen ontwikkelen, een lokaal recidief krijgen of overlijden aan hun ziekte. Voor preventie van mondholtecarcinomen is het bewust maken van niet alleen patiënten maar ook van eerstelijns gezondheidswerkers, zoals huisartsen, tandartsen en mondzorgkundigen, van groot belang. Vooral bewustwording van de voornaamste risicofactoren, zoals alcoholgebruik en roken, is essentieel. Tevens kunnen eerstelijns gezondheidswerkers een grote rol spelen in het stopen met roken of alcoholmisbruik.

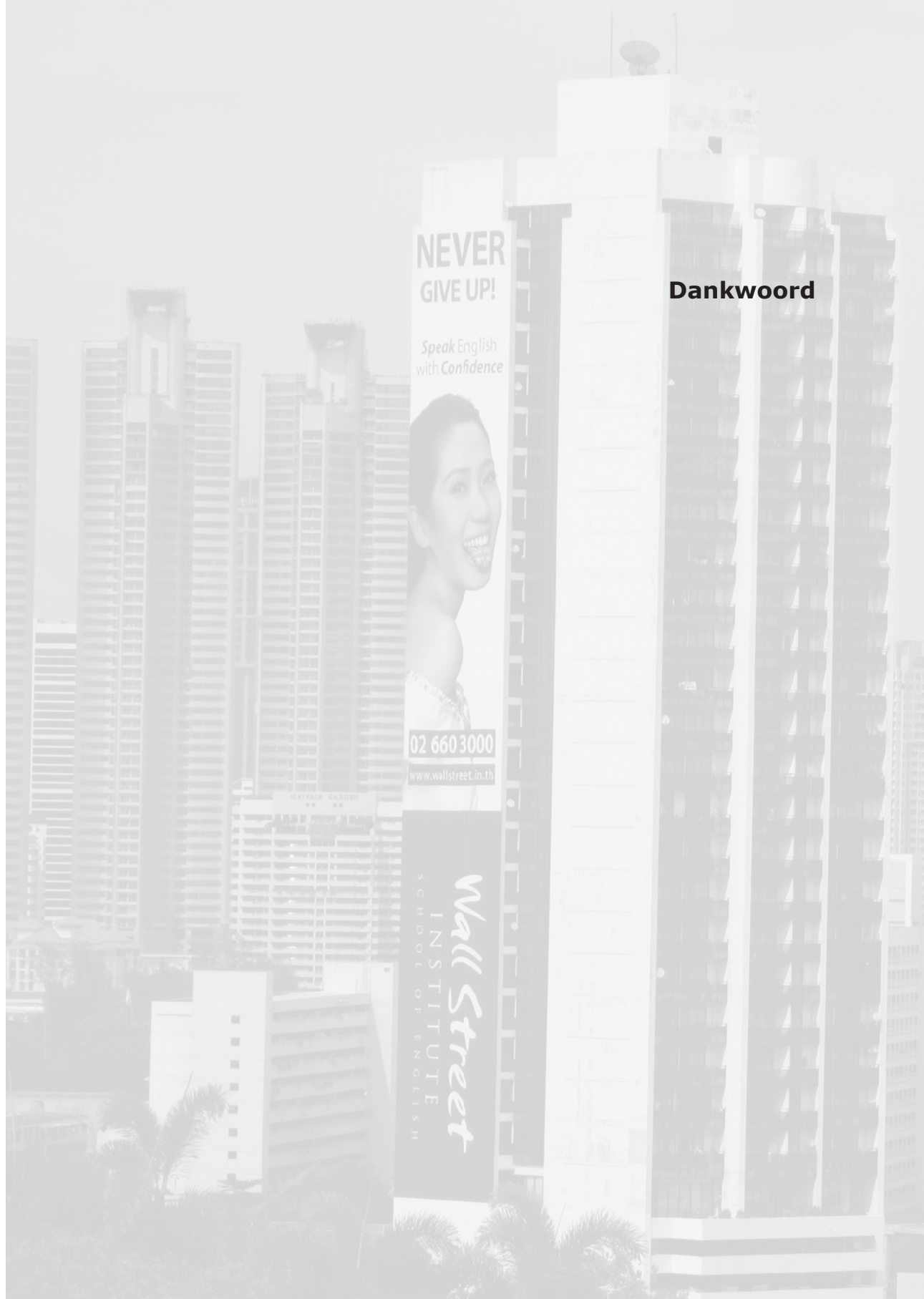
Referenties

1. Nason RW, Binahmed A, Pathak KA, Abdoh AA, Sbndor GKB. What is the adequate margin of surgical resection in oral cancer? Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2009; 107(5):625-629.

2. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncology 2007; 43(8):780-784.

3. Binmadi NO, Basile JR. Perineural invasion in oral squamous cell carcinoma: A discussion of significance and review of the literature. Oral Oncology 2011; 47(11):1005-1010.

4. Lodi G, Sardella A, Bez C, Demarosi F, Carassi A. Interventions for treating oral leukoplakia (Review) 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



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Dankwoord

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Lieve Ūlepanners, Lenie, Peter, Itie, bij jullie ben ik altijd welkom. Balk is een tweede thuis geworden. Mijn tweede 'carriere' als instructeur bij jullie geeft veel ontspanning en plezier. Heel veel dank daarvoor.
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Lieve familie, hartelijk dank voor jullie belangstelling en gezelligheid.

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Caroline, al meer dan 10 jaar delen we lief en leed maar hebben we vooral veel plezier. Dank voor je luisterend oor op moeilijke momenten. Ik hoop nog vele jaren samen te zeilen. Dat je wensen vervuld mogen worden!

Lieve Erik, Puck, Veerle en Adne wat is het fijn om er als 'tante Non' een beetje bij te horen. Ik geniet van die rol en ben erg dankbaar dat er bij jullie altijd plek voor me is (en dan bedoel ik niet alleen aan tafel!).

Petra, hartelijk dank voor je vriendschap, friends are for bad times.

Dear Ruslin, I am very grateful for your friendship. I admire your strength and I am sure Denta Medica will be a great dental hospital one day.

Christiaan en Britta, Remko en Carolina, Viola en Peter, Erik en Puck de banden die op ACTA gesmeed zijn, zijn nog steeds sterk en zijn me dierbaar.

Lieve Mamma, dank voor alle steun. Jij bent mijn rots in de branding. Dit boekje is voor jou en Pappa. Ik ben heel dankbaar voor alle kansen die jullie mij geboden hebben waardoor ik mijn dromen waar kon maken. Ik hoop met jou nog vele verre reizen te kunnen maken, we hebben nog niet alles van Azië gezien!

Curriculum Vitae

Curriculum Vitae

De auteur van dit proefschrift werd op 1 oktober 1973 geboren in Hengelo (O). In 1993 behaalde zij het atheneum diploma aan de Bataafse Kamp te Hengelo. Het tandartsexamen werd in 1998 aan het ACTA (Academisch Centrum Tandheelkunde) behaald. Daarna werd gestart met het Promotie onderzoek op de afdeling Mondziekten en Kaakchrirugie/Orale Pathologie van het VUmc/ACTA te Amsterdam bij Professor van der Waal. In 2001 werd gestart met de opleiding tot Kaakchirurg, deze werd in november 2005 voltooid aan het UMCU, opleiders professor van der Waal en professor Koole. Het artsexamen werd in september 2006 aan het VUMC behaald. Sinds september 2006 is zij als kaakchirurg verbonden aan de maatschap Mondziekten, Kaak- en Aangezichtschirurgie Noord-Holland Noord (Medisch Centrum Alkmaar, Westfries Gasthuis Hoorn, Marina Dental Volendam en het Gemini ziekenhuis te Den Helder).

Speel het spel

Breng je werk in gevaar,
Wees niet de hoofdpersoon.
Zoek de confrontatie maar doe het onopzettelijk.
Vermijd bijbedoelingen.
Verzwijg niet.
Wees week en sterk, wees slim.
Steek je nek uit en veracht de overwinning.
Kijk niet toe, bewijs niets,
maar blijf met alle tegenwoordigheid van geest open voor tekens.
Laat je ogen zien, laat anderen erin kijken.
Zorg voor ruimte en beschouw ieder in zijn eigen perspectief.
Beslis alleen met hartstocht.
Misluk rustig.
Neem vooral de tijd en bewandel zijpaden.
Laat je afleiden, neem om het zo te zeggen vakantie.
Houdt je niet doof, voor geen boom, voor geen water.
Trek je terug in jezelf als je daar zin in hebt en gun je de zon.
Vergeet de mensen in je naaste omgeving.
Verstevig de banden met onbekenden.
Buig je over bijzaken. Wijk uit naar de verlatenheid.
Vermoord het noodlotsdrama, veracht het ongeluk,
analyseer het conflict.
Neem je eigen kleur aan, tot je in je gelijk staat
en het ruisen van de bladeren zoet wordt.
Loop stilzwijgend langs de dorpen.
Ik volg je.

Over de dorpen - Peter Handke