

Chapter 8

Summary and conclusions



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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Unfortunately, the study on the role of DNA-ploidy measurement of J. Sudbö (reference 12 chapter 3) has been withdrawn.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 ($<3\text{mm}$) margins. These findings are in concordance with Binahmed et al,

(2) who found that involved surgical 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

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. Until 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

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