Chapter 7

Summary, conclusions and recommendations
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In chapter 1, a general introduction is given about oral squamous cell carcinoma (OSCC) and oral premalignant disorders with emphasis on oral leukoplakia. Also, a list of definable white diseases and disorders, that may occur in the mouth and that do not carry an increased risk for the development of cancer is shown.

In this thesis, an evaluation was made of the definition of oral leukoplakia, as being proposed by the WHO in 2005. Also the present molecular, clinical and histopathological factors of oral leukoplakia were evaluated, including the follow-up of a cohort of patients after treatment or observation only.

In chapter 2 an evaluation was presented of the definition of oral leukoplakia, proposed by the WHO in 2005, taking into account a previously reported classification and staging system, including the use of a diagnostic Certainty factor of four levels with which the diagnosis of leukoplakia can be established.

In the period 1997-2012 a hospital-based population of 275 consecutive patients with a provisional diagnosis of oral leukoplakia has been examined, 112 men and 163 women, with a mean age of 57 years (range 17-98 years). In only 176 patients of these 275 patients a firm diagnosis of leukoplakia has been established based on strict clinicopathological criteria. A flowchart is presented for the diagnosis of oral leukoplakia. The 176 patients have subsequently been staged using a classification and staging system based on size and histopathological features.

For use in epidemiological studies it seems acceptable to accept a diagnosis of leukoplakia based on a single oral examination (Certainty level 1). For studies on management and malignant transformation rate the recommendation is made to include the requirement of histopathological examination of an incisional or excisional biopsy, representing Certainty level 3 and 4, respectively. The recommendation is made to modify the present WHO definition of oral leukoplakia by adding the requirement of histopathological examination in order to obtain a definitive clinicopathological diagnosis. This recommendation results in the following definition of oral leukoplakia: “A predominantly white lesion or plaque of questionable behaviour having excluded, clinically and histopathologically, any other definable white disease or disorder”. Furthermore, we recommend the use of strict diagnostic criteria for predominantly white lesions for which a causative factor has been identified, e.g. smokers’ lesion, frictional lesion and dental restoration associated lesion.

In chapter 3 an evaluation was made of the definition based on its use in the literature.
of proliferative verrucous leukoplakia (PVL). PVL was first described by Hansen et al. Cerero Lapiedra et al (2010) proposed diagnostic criteria of PVL using a set of major and minor criteria. Some of these criteria are well accepted, but others seem to be somewhat debatable. Therefore, a modified set of criteria has been proposed.

In chapter 4, the treatment results of CO$_2$-laser vaporisation in a well defined cohort of patients with oral leukoplakia were presented.

The group of 35 patients consisted of 10 men and 25 women, with a mean age of 55.5 years (range 26-87 years). Before treatment, a clinical photograph and an incisional biopsy were performed in all cases. Also the posttreatment results were documented with clinical photographs. The assessment of the treatment results was performed by an independent clinician who had not performed the treatment. The mean follow-up period was 61.9 months (range 12 to 179 months).

In 14/35 patients, there was a recurrence between 1 and 43 months (mean 18.7 months), the annual recurrence rate being approximately 8%. In 3 of these patients, malignant transformation occurred at a later stage. In two other patients a malignancy occurred without a prior recurrence. In altogether 5/35 patients malignant transformation occurred in a mean period of 54 months, the annual malignant transformation rate being approximately 3%.

With regard to recurrences, the results in the present study are worse than those reported in the literature, perhaps due to a different use of diagnostic criteria for oral leukoplakia and allied white lesions and perhaps also due to a different way of assessing recurrence. The malignant transformation rate in the present study is more or less comparable with that of other studies.

In chapter 5, the factors that possibly predict malignant transformation in a well defined cohort of patients with a long-term follow-up were reported. All leukoplakias were staged according to a clinicopathological classification and staging system. Furthermore, a diagnostic Certainty factor has been used with which the diagnosis has been established.

The group consisted of 144 patients, 44 men and 100 women with a mean age of 58.7 years (SD= 14.11, range 26-98 years). The size, presence and degree of epithelial dysplasia were incorporated in a clinicopathological classification and staging system. Initial management consisted of surgical excision, CO$_2$ laser vapourisation or observation only. The mean follow-up period was 51.2 months (SD= 39.33, range 12-179 months).

In 16/144 patients (11%) malignant transformation occurred between 20 and 94 months (mean 57.0 months) after the first visit, the annual malignant transformation rate being approximately 2.6%. A large size of the lesion (≥4 cm) showed to be the only
statistically significant predictor of malignant transformation ($p = 0.034$).

A size of $\geq 4$ cm showed to be the only significant predicting factor of malignant transformation in oral leukoplakia. No other epidemiological, etiological, clinical or histopathological parameters were of statistical significance.

In chapter 6, the possible difference between DNA ploidy measurement using either flow cytometry (FCM-DNA) or image cytometry (ICM-DNA) in a well defined cohort of patients with oral leukoplakia has been described. This study is a continuation of the study of Bremmer et al.\cite{bremmer2017}. Relations between DNA ploidy and the histopathological grading and other clinical parameters, such as gender, smoking habit, alcohol consumption, homogeneity, size and location of the lesion have been investigated.

A total of 41 patients have been included, 20 men and 21 women with a mean age of 59 years (range 36–78 years). Nine patients in this cohort overlapped between this study and the study by Bremmer et al.\cite{bremmer2017}. With FCM-DNA, three lesions were aneuploid and with ICM-DNA, 19 lesions were aneuploid. DNA ploidy was compared with clinicopathological and patient parameters. There were no statistically significant differences between DNA ploidy and any patient factor with both FCM-DNA and ICM-DNA. Using FCM-DNA, DNA aneuploid lesions showed statistically significant more dysplasia ($p = 0.04$) than diploid lesions. Furthermore, DNA aneuploid lesions were more frequently encountered at high-risk locations ($p = 0.03$) as being determined with FCM-DNA. These relations were not found when DNA ploidy was determined with ICM-DNA.
Main conclusions and recommendations of this thesis

1. The use of strict diagnostic criteria is recommended for oral leukoplakia and predominantly white lesions for which a causative factor has been identified, e.g. smokers’ lesion, frictional lesion and dental restoration associated lesion.

2. A flowchart (Figure 1) for the diagnosis of oral leukoplakia is presented.

3. For use in studies on treatment results and malignant transformation, the recommendation is made to modify the present WHO 2005 definition of oral leukoplakia by adding the requirement of histopathological examination. As a result, we suggest: “A predominantly white lesion or plaque of questionable risk having excluded, clinically and histopathologically, (other) known diseases or disorders that carry no increased risk for the development of cancer”.

4. For use in epidemiological studies the requirement for histopathological examination to arrive at a diagnosis of leukoplakia may be dropped. As a result, we suggest: “A predominantly white lesion or plaque of questionable risk having excluded, clinically, (other) known diseases or disorders that carry no increased risk for the development of cancer”.

5. The choice of treatment of oral leukoplakia depends on the extent of the lesion, the oral subsite (e.g. floor of mouth) and the presence of dysplasia. In case of dysplasia, active treatment is recommended.

6. CO2 laser vaporisation may be considered in case of location in the floor of the mouth, in lesions larger than 2-3 cm, particularly if not well-circumscribed, and in the absence of moderate or severe dysplasia. It should be remembered that surgical excision has the advantage of enabling histopathologic examination of the entire lesion instead of just an incisional biopsy of part of the lesion.

7. Before CO2 laser vaporisation, an incisional biopsy is required in order to determine the presence and degree of dysplasia.

8. No reliable comparisons can be made between the treatment results of CO2 laser vaporisation and cold knife surgical excision, because of different indications for both treatment modalities guided by oral subsite (e.g. floor of mouth), size of the leukoplakia and histopathological parameters, in particular the presence and degree of epithelial dysplasia.

9. The risk of malignant transformation of oral leukoplakia seems particularly increased in a large size of the lesion (≥4 cm).
10. The exact role of DNA aneuploidy with regard to malignant transformation is still unknown. There is need for a single molecular marker or a set of markers in oral leukoplakia that predicts malignant transformation.

11. As mentioned by Einhorn and Wersäll already in 1967 there is no evidence that the incidence of oral carcinoma can be diminished by surgical removal of the leukoplakia but this does not mean that the operation should be abandoned, mainly for a histological diagnosis.

12. There are no strict guidelines available for the duration and frequency of follow-up examinations. In general, lifelong follow-up examination is advised at 3-6 months intervals both in patients who have been treated for their leukoplakia as in those who have not. However, the efficacy of follow-up programs in oral leukoplakia has never been proven.
Fig. 1 \( C \) = Certainty factor

**DIAGNOSIS OF ORAL LEUKOPLAKIA**
*(Provisional clinical diagnosis, \( C / l \))*

- Possible cause(s)
  - Consider the taking of a biopsy, particularly in case of symptoms
- Elimination of possible cause(s), such as mechanical irritation, amalgam restoration in direct contact with the white lesion, fungal infection, and tobacco habits (maximum 4 weeks to observe the result)

  - No response
    - Biopsy
      - (Definitive clinical diagnosis, \( C 2 \))
    - Definitive clinicopathological diagnosis
      - \( C 3 \) (in case of incisional biopsy only)
      - \( C 4 \) (in case of excisional biopsy or surgical excision after an incisional biopsy)
      - Definable lesion
  - Good response
    - Definable lesion

  - Nondysplastic leukoplakia
  - Dysplastic leukoplakia
Reference List


(2) van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncol* 2009 Apr;45(4-5):317-23.


