ORAL LEUKOPLAKIA

Kees-Pieter Schepman

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A clinicopathological study based on the revised international definition

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VRIJE UNIVERSITEIT

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Promotoren: prof.dr. I. van der Waal
prof.dr. G.B. Snow

Voor mijn ouders

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Voorwoord

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- Chapter 1-

GENERAL INTRODUCTION AND AIM OF THE STUDY

Oral Cancer

The majority, some 80 - 90 per cent, of all malignancies that occur in the oral cavity are oral squamous cell carcinomas. Oral cancer incidence rates vary widely across the world.[1] In the western countries incidence rates for squamous cell carcinoma of the oral cavity are 3 – 4 per 100,000 per year.[2] The onset of oral cancer usually takes place after the age of 40, resulting in a peak incidence after the 7th decade.[2] The gender distribution shows overall a male predominance, however the male-to-female ratio has declined, possibly due to an increase in tobacco and alcohol consumption among women.

Tobacco and alcohol are the two best recognized risk factors for oral cancer in the Western countries, and account for over 75 per cent of oral cancers.[3] Epidemiological data show that approximately 15 per cent of oral and pharyngeal cancers can be attributed to dietary deficiencies, whereas fresh fruits and vegetables may have a protective effect on the development of oral cancer.[3,4] The possible aetiological role of virusses and fungal infections in the development of oral cancer remains controversial.[3,5,6] Poor dentition and oral hygiene appear to be associated with an increased risk for oral cancer.[7-9] Mouthwashes high in alcohol intake may act as an risk factor as well;[10] however, others have shown that there is no support for a causal association between mouthwash use and the risk of oral cancer.[11] Increased rates due to occupational factors may play a small role, and have been reported among workers exposed to asbestos, mineral fibers, and several other substances.[3] Epidemiological data show only a slight increase in the risk for oral cancer among persons with family members with oral cancer.[12] However, individual susceptibility may vary due to polymorphisms in p450 genes that metabolize tobacco and other carcinogens.[13,14] Oral cancer may also develop from precursor lesions, so called premalignant or, synonymously, potentially malignant, or precancerous lesions. The frequency of malignant transformation of oral leukoplakia, the most frequent and best known premalignant lesion, varies between 0 and 20 per cent in an observation period of 1 – 30 years.[15-25] The treatment modality of a histologically proven oral squamous cell carcinoma varies. Early disease is treated either by surgery and/or radiotherapy.[26] The choice between these two modalities mainly depends on the size and the localisation of the tumor. The prognosis largely depends on the stage of the tumor. Small tumors have a better prognosis than more advanced tumors. For instance, for cancer of the tongue the five-year survival rates vary between 60 % for T1 and 25 % for T4 lesions. Inspite of many efforts in prevention and therapy, long-term survival rates have not improved substantially over the last 30 years.[27]

As oral cancer may develop from premalignant lesions, as mentioned above, the management of these (premalignant) lesions may prevent a certain amount of cancers of the oral cavity.

Premalignant, precancerous or potentially malignant lesions

Oral leukoplakia and erythroplakia are regarded to be a premalignant or, synonymously, a potentially malignant or precancerous lesion. A precancerous lesion is defined as a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart.[28]

In 1978, a World Health Organization group defined leukoplakia as: "A white patch or plaque that cannot be characterized, clinically or pathologically, as any other disease." It was emphasized that the term leukoplakia should carry no histological connotation and should be used only in a descriptive clinical sense.[29]

In 1983, at an international seminar, leukoplakia was redefined as: "A white patch or plaque of the oral mucosa that cannot be characterized clinically or pathologically as any other disease and it is not associated with any physical or chemical causative agent except the use of tobacco".[30] It was decided to avoid the term leukoplakia in case of a known aetiological factor, except in those cases where tobacco was believed to be the cause. The definition resulted in a proposal for an aetiological as well as a clinical description for oral leukoplakia. The aetiological description identified two categories: leukoplakias with unknown aetiology (idiopathic) and those associated with, or thought to be caused by the use of tobacco (tobacco-associated). Whitish patches for which a local cause could be identified were listed according to the known cause and not designated as leukoplakias.

Because of the identification of difficulties in interpretation and application of the previous definitions, e.g. with regard to the degree of whiteness of the lesion, or the inclusion of the term "pathologically", which was a retraint for epidemiologically studies, an international symposium was held in 1994, in order to further clarify this subject.[31] Oral leukoplakia has been defined since then as "A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion". A distiction was made between a provisional and a definitive diagnosis. A provisional diagnosis is made when a lesion at clinical examination cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance. A definitive diagnosis is made as a result of the identification, and if possible elimination, of suspected aetiological factors, and in the case of persistent lesions, histopathological examination.

The term 'erythroplakia' is used analogously to leukoplakia to designate lesions of the oral mucosa that present as red areas and cannot be diagnosed as any other definable lesion.[31]

Aim and outline of the study:

Various attempts have been made during the last three decades to achieve a consensus on the definition of oral leukoplakia. For clinicopathological studies on oral leukoplakia it is clearly relevant to have consistency of diagnosis in

order to enable comparative assessments between preventive or clinical management protocols.[31] The aim of the studies presented in this thesis was to investigate the implications of a revised definition of oral leukoplakia in a clinical and pathological setting, and to gain more insight into the biological behaviour in order to develop a management protocol for this premalignant lesion.

Chapter 2 gives a review of the literature on oral leukoplakia from a clinocopathological point of view. The implications of the revised definition of oral leukoplakia will be discussed with respect to the management of this premalignant lesion.

The premalignant potential of oral leukoplakia may be related to aetiological, topographical, clinical or histological characteristics. Features such as size of the leukoplakia, site, clinical aspect, and histopathologic aspects have been incorporated into a classification and staging system. The classification and staging system has primarily been developed to make comparative assessments between studies on oral leukoplakia more accurate. In **chapter 3** a classification and staging system for oral leukoplakia is introduced and the initial experiences with this new classification and staging system based on 100 patients with oral leukoplakia are described. In the same chapter a proposal for a revision of the classification and staging system is put forward.

A restraint for epidemiological studies, which might take place under various circumstances under which patients may be examined, was the inclusion of the word 'pathologically' in one of the previous definitions of oral leukoplakia, which suggested that the diagnosis leukoplakia could not be made without a biopsy. In the new definition of oral leukoplakia a distinction is made between a provisional diagnosis, which is made at a clinical level and a definitive diagnosis, which requires the exclusion of possible aetiological factors and, if the lesion persists, histopathological examination. The experiences and implications of the new definition of oral leukoplakia, using a provisional and a definitive diagnosis, are described in **chapter 4** in a prevalence study on oral white lesions.

The precancerous nature of oral leukoplakia is based on the fact that some leukoplakias transform into cancer.[31] In **chapter 5** the subject of malignant transformation of oral leukoplakia is investigated in a follow-up study of a hospital-based population of 166 patients with oral leukoplakia.

There is an ongoing debate on the prevalence of associated precancerous lesions at the time of diagnosis of an oral squamous cell carcinoma. In **chapter 6** a study is described determining the presence of concomitant leukoplakia in 100 consecutive patients with oral squamous cell carcinoma.

Tobacco usage is the most important known aetiological factor in the development of oral leukoplakia. Some white lesions, such as palatal keratosis in reverse smoker's, and snuff dipper's lesions, referred to as 'tobacco-induced white lesions' are clearly related to tobacco usage and may show a distinct

anatomical relation to the tobacco product used.[31] In **chapter 7** we investigated the possible relationship between smoking cigarettes, cigars, or pipes on the anatomical distribution of oral leukoplakia, i.e. referred to as tobacco-associated leukoplakias, based on a population of 146 patients with oral leukoplakia.
Finally, in the last chapter, a summary and recommendations with respect to the diagnosis and management for oral leukoplakia are presented, including a modified flow diagram and modified classification and staging system.

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- Chapter 2 -

ORAL LEUKOPLAKIA: A CLINICOPATHOLOGICAL REVIEW

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Abstract
Leukoplakia is the most common premalignant or potentially malignant lesion of the oral mucosa. It seems preferable to use the term leukoplakia as a clinical term only. When a biopsy is taken, the term leukoplakia should be replaced by the diagnosis obtained histologically. The annual percentage of malignant transformation varies in different parts of the world, probably as a result of differences in tobacco and dietary habits. Although epithelial dysplasia is an important predictive factor of malignant transformation, it should be realized that not all dysplastic lesions will become malignant. On the other hand non-dysplastic lesions may become malignant as well. In some parts of the world the tongue and the floor of the mouth can be considered to be high-risk sites with regard to malignant transformation of leukoplakia, while this does not have to be the case in other parts of the world. The cessation of tobacco habits, being the most common known aetiological factor of oral leukoplakia, has been shown to be an effective measure with regard to the incidence of leukoplakia and, thereby, the incidence of oral cancer as well. Screening for oral precancer may be indicated in individuals at risk.

Introduction

The present review of oral leukoplakia is largely based on personal experience both with the clinical and histopathological aspects, and on the literature about this subject during the last 30 years, without an attempt at complete coverage.
Owing to the influence that tobacco habits and dietary products may have on the oral mucosa, including oral leukoplakia, may show geographical and ethical differences, both with regard to the clinicopathological appearances and biological behaviour.

Definition and terminology

Leukoplakia
Oral leukoplakia has recently been redefined as "a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakias will transform into cancer".[1] In that report, a distinction was made between a provisional diagnosis of oral leukoplakia and a definitive one. A provisional diagnosis is made when a lesion at clinical examination cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance; a definitive diagnosis of oral leukoplakia is made as a result of the identification, and if possible elimination, of suspected aetiological factors and, in the case of persistent lesions, histopathological examination.[1] When the whiteness is not very distinct, the term preleukoplakia is sometimes used, not to be confused with leukoedema.
Histopathological examination of a clinically diagnosed leukoplakia serves two purposes: (1) to exclude any other definable lesion, e.g. lichen planus; and (2) to establish the degree of epithelial dysplasia, if present. In the presence of carcinoma-in-situ or invasive carcinoma the clinical diagnosis of leukoplakia is replaced by the diagnosis obtained histologically.[2,3] It seems preferable to follow the same concept in case of other histological findings, particularly with regard to the presence or absence of epithelial dysplasia. As a result, one may then recognize a (white) non-dysplastic or dysplastic lesion. In that way, the term leukoplakia remains a clinical term only and its use thus carries no implications with regard to the histological findings, which is in accordance with previous recommendations.[2,3]

Definable white lesions
In the various definitions of oral leukoplakia reference is made to "other diseases" or "definable lesions".[1-3] In daily practice the clinical and histopathological features of white oral lesions are not always characteristic; a number of cases cannot be classified with certainty as a "definable lesion".
A few of the white lesions listed in Table 1 deserve further attention with regard to definition and terminology.

Table 1: The most common definable white or predominantly white lesions of the oral mucosa and their main diagnostic criteria

Lesion	Main diagnostic criteria
Candidiasis, pseudomembranous*	Clinical aspect (pseudomembranes, often symmetrical pattern)
Discoid lupus erythematosus	History of skin lesion; clinical appearance (incl. bilateral pattern); histopathology
Frictional lesion	Presence of mechanical irritation (e.g. habit of vigorous toothbrushing)
Hairy leukoplakia ("Greenspan lesion")	Clinical aspect (incl. bilateral localisation on the tongue); histopathology (incl.EBV)
Lesion associated with dental restoration (incl. 'galvanic lesion')	Clinical aspect (relation to dental restoration)
Leukoedema	Clinical aspect (incl. symmetrical pattern)
Lichen planus, reticular and plaque type	Clinical aspect (often symmetrical pattern); histopathology
Linea alba	Clinical aspect (incl. location on line of occlusion in cheek mucosa)
Morsicatio (habitual chewing or biting of the cheeks, tongue, lips)	History of habitual biting or chewing; clinical aspect
Papilloma and allied lesions	Clinical aspect; histopathology
Syphilis, secondary ("mucous patches")	Clinical aspect; demonstration of T.pallidum; serology
Tobacco-induced lesions	
- Smoker's palate	Clinical aspect; history of smoking
- Palatal lesions in reverse smoking	Clinical aspect; history of reverse smoking
- Snuff dipper's lesion	Clinical aspect; site where snuff is placed
White sponge nevus	Family history; clinical aspect (often symmetrical pattern)

* There is no consensus in the literature whether or not to recognize a hyperplastic subtype of oral candidiasis.

Hyperplastic candidiasis versus Candida-associated leukoplakia. There is no consensus in the literature whether or not to recognize a hyperplastic subtype of candidiasis. When dealing with a hyperplastic epithelial lesion in which the presence of Candida albicans is demonstrated, some authors prefer to refer to such lesions as Candida-associated leukoplakias while others prefer the term hyperplastic candidiasis.[4] In the absence of clinical response to antifungal treatment it seems preferable to consider such lesion a leukoplakia.

Hairy leukoplakia ("Greenspan lesions"). The term "hairy leukoplakia" is unfortunate for several reasons. First of all, hairy leukoplakia is a definable lesion.[5,6] Furthermore, the lesion is not a premalignant one. Therefore, the use of the term hairy leukoplakia should be abandoned. As an alternative, the term "Greenspan lesion" has been suggested.[7]

Tobacco-induced white lesions. Smoker's palate ("leukokeratosis nicotina palati"), palatal keratosis in reverse smokers, and snuff dippers' lesions are clearly related to tobacco use and, therefore, are usually listed as "tobacco-induced lesions".[1,2] These lesions are being regarded as "definable lesions" and are traditionally not described as leukoplakia.[8] Nevertheless, some of these lesions may transform into cancer. Apparently, this is not the case for smoker's palate, while it is for palatal lesions in reverse smokers. The possible premalignant nature of snuff depends on the type of snuff and possibly also on other factors, such as various ingredients that may have been added to the snuff.[9-11]

Tobacco-associated leukoplakia; idiopathic leukoplakia. With regard to white lesions other than the tobacco-induced white lesions mentioned previously, the aetiological role of tobacco in patients who smoke cigarettes, cigars or pipes is less obvious.[12,13] Therefore, preference has been given to the term "tobacco-associated leukoplakia" (leukoplakia in smokers) above the term "tobacco-induced white lesion".[2] As a result, one also recognizes non-tobacco associated leukoplakia (leukoplakia in non-smokers), often referred to as idiopathic leukoplakia. Whether this subtyping is of any clinical relevance, is still to be determined. Furthermore, the issue becomes even more complex in case of mixed habits of tobacco chewing and smoking.

Premalignant, precancerous or potentially malignant lesion

Oral leukoplakia is regarded to be a premalignant or, synonymously, a potentially malignant or precancerous lesion. A precancerous lesion has been defined as a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart.[14]

However, no odd ratios have been mentioned in the literature that would define "more likely to occur".

In two studies from India, rather low annual malignant transformation rates of oral leukoplakia have been reported, 0.3%[15] and a 0.06% respectively.[16] In reports from Western countries, usually based on hospital material, somewhat

coexist.[47] Therefore, a note should be added to the histopathological report that some of the exophytic, verrucous or papillomatous lesions, in spite of the absence of epithelial dysplasia, may in time progress to squamous cell carcinoma and that long-term follow-up should be considered.
At times, it may be difficult to arrive at or to exclude one of the definable lesions mentioned in Table 1. The final diagnosis of a white lesion of the oral mucosa can often only be made through a close dialogue between the clinician and the pathologist. Even then, cases may remain unsettled.

Grading of epithelial dysplasia
Based on the histopathologist's interpretation of the presence of dysplastic features, epithelial dysplasia is usually divided into three categories: mild, moderate and severe. It has been observed that the degree of epithelial dysplasia correlates with the age of the patient.[59]
Until now, it has not been possible to devise a scheme for grading epithelial dysplasia that gives consistent and reproducible results[60-63], the main reason being the subjectivity of the assessment of the components of epithelial dysplasia as listed in Table 2. There may be, indeed, a strong interobserver discrepancy between pathologists in the evaluation of the presence and the degree of epithelial dysplasia.[61,63] Nevertheless, it is recommended that the histological report of a leukoplakia should include a statement on the absence or presence of epithelial dysplasia and an assessment of its severity.[2]
To some extent, the practical value of the grading of epithelial dysplasia is questionable. Although leukoplakias with moderate or severe epithelial dysplasia show a greater disposition for malignant transformation than in the absence of dysplastic features, carcinomatous transformation may also take place in non-dysplastic leukoplakias.[19,46,64-66]

Other examination techniques
In a review of advanced methods in the evaluation of premalignant lesions of the oral mucosa, it was concluded that the assessment of the biological potential of precancerous lesions still mainly relies on light microscopic histologic examination.[64] Nevertheless, there are many recent publications on promising new biological risk markers.[41,67-100]

Malignant transformation
Certain features have been reported to be associated with an increased risk of malignant transformation. These are, in arbitrary order: (1) gender, particularly women seem to be at risk; (2) long duration of the leukoplakia; (3) leukoplakia in non-smokers (idiopathic leukoplakia); (4) location in the floor of the mouth or/and on the tongue; (5) non-homogeneous type; (6) presence of *C. albicans*; and (7) presence of epithelial dysplasia.

Clinical aspects
Leukoplakias may occur either as a single, localized change of the oral mucosa or as diffuse, often multiple, lesions. The site distribution shows world-wide differences, that are partly related to gender and tobacco habits.[15,16,18,42] In fact, any oral site may be affected.
In general, two clinical variants of leukoplakia are being recognized, the homogeneous and the non-homogeneous type. Transitions or changes among the different clinical variants of oral leukoplakia may occur.[43,44]
Homogeneous leukoplakia has been defined as a predominantly white lesion of uniform flat, thin appearance that may exhibit shallow cracks and has a smooth, wrinkled or corrugated surface with a consistent texture throughout.[1] It should be emphasized that the adjective "homogeneous" not only applies to the homogeneous whitish colour of the lesion, but above all, to a flat, thin, and rather smooth surface. It does not apply to verrucous, papillary or exophytic lesions that otherwise may have a homogeneous colour or texture. Those lesions are considered non-homogeneous leukoplakias.
Non-homogeneous leukoplakia has been defined as a predominantly white or white-and-red lesion ("erythroleukoplakia") that may be irregularly flat, nodular or exophytic. The nodular lesions are characterized by white patches or nodules on an erythematous base[45], while the exophytic lesions have irregular blunt or sharp projections.[1] The adjective "non-homogeneous" is applicable both to the aspect of colour, i.e. a mixture of white and red changes ("erythroleukoplakia") and to the aspect of texture, i.e. exophytic, papillary or verrucous. With regard to the latter lesions, no reproducible clinical criteria can be provided to distinguish (proliferative) verrucous leukoplakia from the clinical aspect of verrucous hyperplasia or verrucous carcinoma.[46,47] Furthermore, a diagnosis of proliferative verrucous leukoplakia can only be made retrospectively after new lesions have developed.[48]
The homogeneous type is usually otherwise asymptomatic, whereas the non-homogeneous (mixed white and red) leukoplakias are often associated with mild complaints of localized pain or discomfort. In the presence of redness or palpable induration, malignancy may be present already.

Diagnostic procedures
Elimination of possible cause(s)
When faced with a patient with a white lesion of the oral mucosa, the clinician will first try to rule out any of the definable white lesions listed in Table 1 before accepting a definitive clinical diagnosis of leukoplakia. For instance, in the case of a non-homogeneous white and red lesion, the result of antifungal treatment may be awaited for a period of 2-4 weeks. A 2-4 week interval to

higher figures have been mentioned.[17-25] As stressed by Gupta et al.[15,26] ,one must take into account, when studying percentages of malignant transformation rates of oral leukoplakia: (1) the length of observation period; (2) the type of study population; and (3) the therapeutic approach.
On the basis of the lowest reported annual malignant transformation rate of oral leukoplakia, it can be calculated that patients with oral leukoplakia carry a 5-fold higher risk of developing oral cancer than controls.[16] Whether this increased risk is sufficiently high to meet the criteria of "more likely to occur", as mentioned in the definition of a precancerous lesion, remains an open question.

Epidemiology

Incidence and prevalence

In a 10 year prospective study in India in large random samples, carried out in several geographic areas with various kinds of tobacco usage, the annual age-adjusted *incidence* rates of leukoplakia per 1,000 population per year varied from 1.1 to 2.4 among men and from 0.2 to 1.3 among women; the *prevalence* varied from 0.2 to 4.9%.[15] In an adult Swedish population a 3.6% *prevalence* rate was recorded.[27]

Age and gender

The onset of leukoplakia usually takes place after the age of 30 years, resulting in a peak incidence above the age of 50 years, as shown in a large sample of leukoplakia with a data resource based on surgical pathology reports.[28]
The gender distribution in most studies varies, ranging from a strong male predominance in different parts in India, to almost 1:1 in the Western world.

Aetiology

The possible role of tobacco has been previously mentioned. Whether the use of alcohol by itself is an independent aetiological factor in the development of oral leukoplakia, is still questionable.[29-33]
The role of *C. albicans* as a possible aetiologic factor in leukoplakia and its possible role in malignant transformation is still unclear.[34-37] In recent years, the possible contributory role of viral agents in the pathogenesis of oral leukoplakia has also been discussed, particularly with regard to exophytic, verrucous leukoplakia.[38,39]
In a study from India, serum vitamin levels of vitamin A, B_{12}, C, beta carotene and folate acid were significantly decreased in patients with oral leukoplakia compared to controls, whereas serum vitamin E was not.[40] Fresh fruits and vegetables may have a protective effect in the primary prevention of oral cancer and precancer.
Relatively little is known yet with regard to possible genetic factors in the development of oral leukoplakia.[41]

Histopathological aspects

The histopathological aspects of leukoplakia may vary from atrophy of the epithelium to hyperplasia with or without hyperkeratosis. Epithelial dysplasia, if present, may range from mild to severe. In some instances carcinoma *in situ* and even squamous cell carcinoma are encountered histologically.
The various cellular changes that may occur in epithelial dysplasia are listed in Table 2. Some authors consider a change in the microvascularisation and/or an increase in the number of subepithelial lymphocytes, plasmacells, Langerhans' cells and interepithelial cells, and the presence of Candida organisms additional indicators of dysplasia. The clinical significance of human papillomavirus-associated epithelial dysplasia, so-called koilocytic dysplasia, remains to be investigated.[53] Dysplastic epithelium may show features that to some extent resemble those of lichen planus; some authors refer to such an event as "lichenoid dysplasia".[54]
In the presence of the use of tobacco often so-called chevron type of keratinization is observed.[55,56] Exocytosis of inflammatory cells in the epithelium is uncommon. In the presence of *C. albicans* the formation of microabcesses may be observed in the superficial layers of the epithelium.

Table 2: Commonly used histopathological features of epithelial dysplasia[3]

1. Loss of polarity of the basal cells;
2. Presence of more than one layer of cells having a basaloid appearance;
3. Increased nuclear - cytoplasmic ratio;
4. Drop-shaped rete processes;
5. Irregular epithelial stratification;
6. Increased number of mitotic figures (a few abnormal mitoses may be present);
7. Presence of mitotic figures in the superficial half of the epithelium;
8. Cellular pleomorphism;
9. Nuclear hyperchromatism;
10. Enlarged nucleoli;
11. Reduction of cellular cohesion;
12. Keratinization of single cells or cell groups in the prickle layer.

White or whitish lesions that clinically and/or histopathologically have an exophytic, verrucous or papillomatous architecture and in which no distinct signs of epithelial dysplasia are present at the light microscopic level, may progress to squamous cell carcinoma. It is beyond the scope of this paper to discuss in detail the histopathological aspects of verrucous carcinoma, verrucous hyperplasia and papillary squamous cell carcinoma and the difficulty one may have to distinguish these entities from each other, if possible at all. For instance, some consider verrucous hyperplasia an early stage of verrucous carcinoma.[57,58], while others do make a distinction between verrucous hyperplasia and verrucous carcinoma, but notice that these entities may

coexist.[47] Therefore, a note should be added to the histopathological report that some of the exophytic, verrucous or papillomatous lesions, in spite of the absence of epithelial dysplasia, may in time progress to squamous cell carcinoma and that long-term follow-up should be considered.
At times, it may be difficult to arrive at or to exclude one of the definable lesions mentioned in Table 1. The final diagnosis of a white lesion of the oral mucosa can often only be made through a close dialogue between the clinician and the pathologist. Even then, cases may remain unsettled.

Grading of epithelial dysplasia
Based on the histopathologist's interpretation of the presence of dysplastic features, epithelial dysplasia is usually divided into three categories: mild, moderate and severe. It has been observed that the degree of epithelial dysplasia correlates with the age of the patient.[59]
Until now, it has not been possible to devise a scheme for grading epithelial dysplasia that gives consistent and reproducible results[60-63], the main reason being the subjectivity of the assessment of the components of epithelial dysplasia as listed in Table 2. There may be, indeed, a strong interobserver discrepancy between pathologists in the evaluation of the presence and the degree of epithelial dysplasia.[61,63] Nevertheless, it is recommended that the histological report of a leukoplakia should include a statement on the absence or presence of epithelial dysplasia and an assessment of its severity.[2]
To some extent, the practical value of the grading of epithelial dysplasia is questionable. Although leukoplakias with moderate or severe epithelial dysplasia show a greater disposition for malignant transformation than in the absence of dysplastic features, carcinomatous transformation may also take place in non-dysplastic leukoplakias.[19,46,64-66]

Other examination techniques
In a review of advanced methods in the evaluation of premalignant lesions of the oral mucosa, it was concluded that the assessment of the biological potential of precancerous lesions still mainly relies on light microscopic histologic examination.[64] Nevertheless, there are many recent publications on promising new biological risk markers.[41,67-100]

Malignant transformation
Certain features have been reported to be associated with an increased risk of malignant transformation. These are, in arbitrary order: (1) gender, particularly women seem to be at risk; (2) long duration of the leukoplakia; (3) leukoplakia in non-smokers (idiopathic leukoplakia); (4) location in the floor of the mouth or/and on the tongue; (5) non-homogeneous type; (6) presence of *C. albicans*; and (7) presence of epithelial dysplasia.

Of the above mentioned factors, the presence of epithelial dysplasia - more or less correlating with a clinical non-homogeneous, erythroleukoplakic subtype - seems to be the most important indicator of malignant potential. It is generally accepted that dysplastic lesions carry a 5-fold greater risk than non-dysplastic ones. Nevertheless, it should be recognized that in an Indian study in a mean follow-up observation period of 7 years, some 60% of the dysplastic lesions remained clinically unchanged or even showed complete regression.[15] In fact, only some 7% of the dysplastic lesions progressed to cancer in a mean observation period of 7 years. Others have reported similar findings.[101] As has been mentioned previously, carcinomatous transformation may also take place in non-dysplastic lesions.
Although the presence of *C. albicans* has been indicated as a risk factor[35,36], it is remarkable that this microorganism seems to be particularly present in leukoplakias at the commissures and at the dorsum of the tongue. These sites are rather rare for squamous cell carcinomas to occur and at the same time are common sites for leukoplakia.
In several studies on malignant transformation, particularly from the Western world, the borders of the tongue and the floor of the mouth have been mentioned as so-called high-risk sites. A good example is a paper on sublingual keratosis in which a high malignant transformation rate of homogeneous leukoplakia of the floor of the mouth was discussed, initially showing only hyperkeratosis without epithelial dysplasia.[102] However, in other parts of the world, subsites other than the borders of the tongue and the floor of the mouth may be considered high-risk sites.[15,16]
It is beyond the scope of this treatise to discuss in depth the question of what percentage of oral squamous cell carcinomas arises from pre-existing lesions, particularly from leukoplakia. Figures from Japan and the Western world range from 17%[103] to approximately 35%[104], respectively.

Management
General considerations
As has been discussed previously, management of white oral lesions is primarily directed towards the elimination of possible causative factors, e.g. friction, *C. albicans*, thus ruling out other definable lesions (Table 3). In persisting lesions or in the absence of possible causative factors, a biopsy should be taken to exclude, histologically, the presence of a definable lesion and to establish the degree of epithelial dysplasia, if present, or even the presence of carcinoma or carcinoma *in situ*.
It is an ethical question whether or not it would be justified in case of persisting tobacco habits to delay active treatment of oral leukoplakia, without histological evidence of malignancy, as long as the patient has not given up those habits.
In case of mild or absent epithelial dysplasia, the decision whether or not to treat may be influenced by the oral subsite. In the presence of moderate or

severe epithelial dysplasia, active treatment is usually instituted. Some authors recommend treatment of each oral leukoplakia, irrespective of the degree of epithelial dysplasia or the absence of epithelial dysplasia and irrespective of the oral subsite.[22] On the other hand, one might consider limiting treatment to those cases with distinct signs of malignancy. It has been suggested that mucosal carcinomas associated with leukoplakia provide a better prognosis than "*de novo*" carcinomas.[104] Nevertheless, some of these patients will die of their cancer. It remains an open question whether early, active treatment of the leukoplakia in such cases would truly have prevented the occurrence of cancer, and whether or not the morbidity of routine treatment of all patients with oral leukoplakia outweigh the death of a limited number of patients.

There are instances where active treatment of oral leukoplakia hardly can be instituted. This is especially true in extensive leukoplakia that involves more or less the entire oral mucosa. Also patient factors may hinder optimum treatment. Older age in itself does not seem to be a good delineator to decide whether or not to treat a leukoplakia that would otherwise require treatment. In oral leukoplakia in young patients perhaps a more active treatment strategy is required, because of the longer life expectancy.

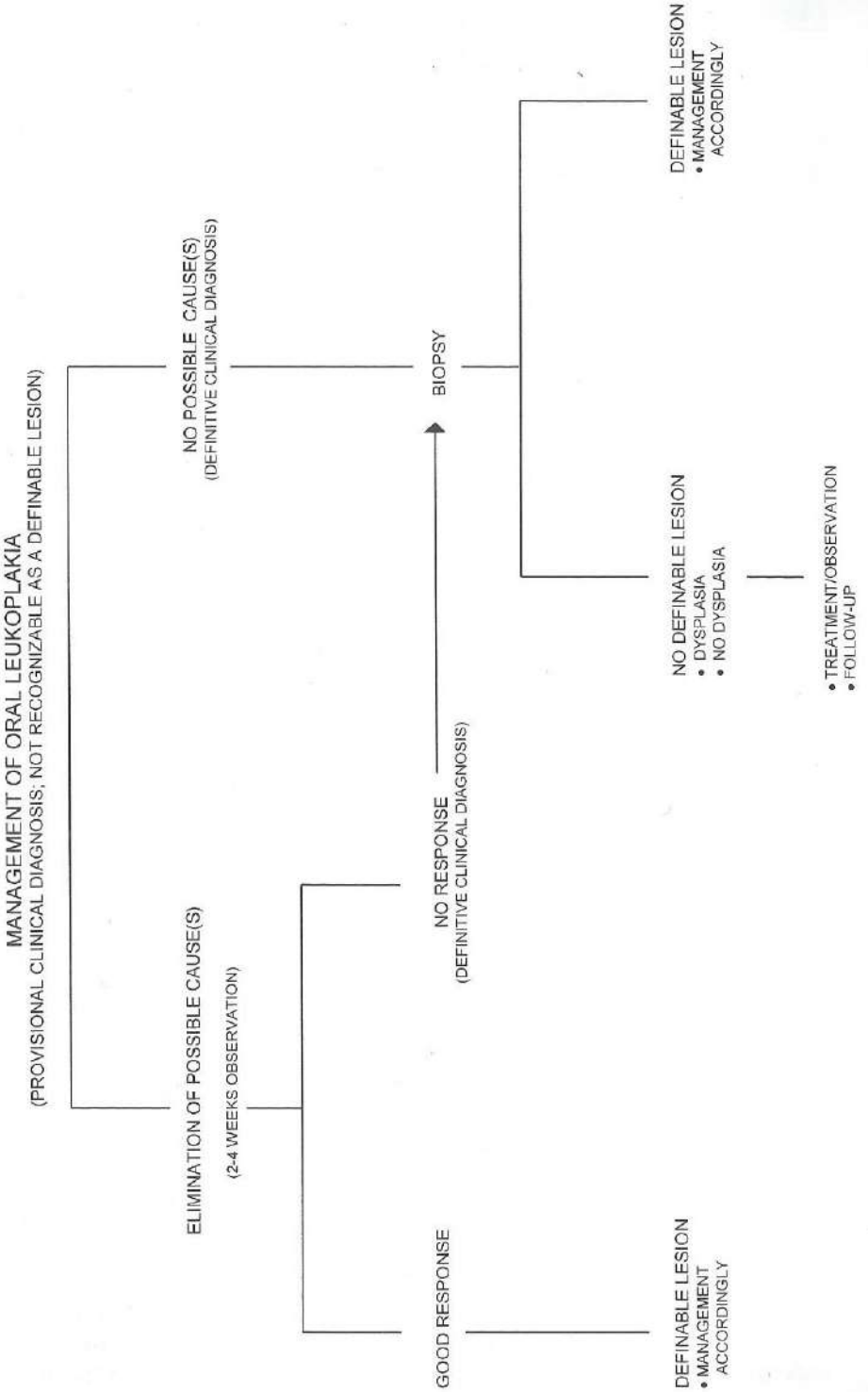
Treatment modalities

Apart from surgical excision, various treatment modalities are available, such as cryosurgery, CO_2-laser surgery, retinoids and other drugs, and, recently photodynamic therapy.[105-108] The latter treatment modality will not be taken into account here because of its rather recent application with regard to oral leukoplakia, not allowing comment on long-term results.

Surgical excision. Traditionally, the recommended treatment for oral leukoplakia, with or without epithelial dysplasia, has been surgical excision. Recurrence rates vary from 20 to 35%.[109] Recurrences are often located adjacent to the previous excised lesion, particularly in case of lesions in the floor of the mouth. Difficulties in determining the proper margin of the lesion and dysplastic epithelium extending into salivary ducts after the surgical excision of the lesion are possible explanations for the comparatively high recurrence rate in these cases.[109-111]

Cryosurgery. The effects of therapeutic freezing upon oral lesions have been studied since the early 1960's. The results of treatment vary. Apart from the advantage as an easily applicable outpatient technique, the most important disadvantages are the lack of visual control over the extent in depth of the cryosurgical treatment, the unavailability of an intact specimen for additional histopathological examination and the often occurring pain and edematous swelling in the first two postoperative weeks. With the present availability of CO_2-laser surgery, there is hardly any place anymore for cryosurgery in the treatment of oral leukoplakia.

Table 3: Diagnosis and management of oral leukoplakia



CO_2- laser surgery. CO_2-laser surgery can be used to treat leukoplakia either by excision of the lesion and part of the underlying tissue, or by evaporation of the surface epithelium. In the latter case, a biopsy should be taken first.
When the added benefits of magnification and precise beam control provided by a microscope are considered, CO_2-laser excision permits the possibility of obtaining the entire lesion for histological examination, although the quality of the surgical margins may be slightly jeopardized by CO_2-laser excision. When compared with cold knife excision, the CO_2-laser has certain advantages, especially when large areas of the epithelium are involved. Morbidity is reduced because of the physical properties of laser energy, healing by secondary intention and epithelial regeneration. This minimizes wound contraction and impairment of functions due to scar formation.
The recurrence rates vary from 9 to 22%.[112,113] In a retrospective evaluation of 167 consecutive patients with oral leukoplakias, there were 69 unfavourable events within 5 years: 31 recurrences, 27 new lesions, 5 carcinomas and 6 other neoplasms elsewhere.[112]
Vitamin A, retinoids, beta-carotene, vitamin E, bleomycin, alpha-tocopherol. It has been shown that oral leukoplakia can be successfully treated with vitamin A.[114] Disadvantage of vitamin A acid and its derivates is its toxicity, necessitating reduction of the dose or temporary abstinence of the drug.[115] Adverse reactions comprise cheilitis, facial erythema, dryness and peeling of the skin, conjunctivitis, photophobia and hypertriglyceridemia. Beta-carotene and vitamin E are considerably less toxic than 13-cis-retinoid acid.[116] The patterns of response and relapse in several studies in which anti-oxidant nutrients have been used are quite similar, showing partial and complete remission in 40-60% of the cases.[117-123]
The topical application of bleomycine is still in an experimental phase.[124-127] The same holds true with regard to the systemic use of alpha-tocopherol.[128,129] Synthetic retinoid N-(4-hydroxyphenyl)-retinamide (4-HPR) in a dosage of 200 mg. daily, applied topically, may be effective in the prevention of recurrence of leukoplakia after surgical excision.[130,131]
The major drawback for most current agents is the recurrence of lesions when treatment is discontinued.[132]

Follow-up
The risk of malignant transformation is not completely eliminated by any of the above described treatment modalities. Spreading and malignant transformation of the lesion may take place in spite of treatment, while the number of lesions prevented from malignant development is unknown.[104] Some verrucous leukoplakias have a strong tendency to recur after conservative surgical excision, being referred to as the previously discussed proliferative verrucous leukoplakia. On the other hand, some leukoplakias may in time regress or

disappear in patients who had no specific treatment and no alteration in habit.[12,13,15,16,19]
No strict guidelines can be given with regard to duration and frequency of follow-up examinations. In general, long term follow-up examination is advised at 6-12 months intervals in patients who have not or not successfully been treated for their leukoplakia.[133,134] Patients who, after treatment, remain disease free for 3 years need perhaps no longer be followed-up.

Prevention and screening
To assess the feasibility of primary prevention of oral cancer, two cohorts were studied in base-line surveys and then followed-up annually for 10 years in the Ernakulam district of Kerala state. The intervention cohort consisted of 12,212 tobacco users aged 15 years and over, who were exposed to a concentrated program of education against tobacco use. The control cohort was a non-concurrent cohort of 6,075 tobacco users studied using similar methods, but with a minimal amount of advice against tobacco use. The stoppage of tobacco use increased and the incidence rate of leukoplakia decreased significantly and substantially in the intervention cohort compared to the control cohort. The decrease in the incidence of leukoplakia was indicative of the decrease in the risk of oral cancer since the two were intimately related. This study demonstrated the feasibility of primary prevention of oral precancer and cancer.[135,136] Therefore, primary health care workers are encouraged to carefully search the mouth for signs of malignancies and possible precursor lesions, and to encourage a healthy life style, particularly with regard to the abstinence of tobacco habits.[137]
Screening is based on the assumption that early diagnosis of precursor lesions (leukoplakia) or small invasive lesions will allow effective treatment to be instituted early and will reduce the overall morbidity and mortality. Screening programmes for oral cancer and precancer may be indicated in individuals at risk, such as predetermined age and risk habits (tobacco and/or alcohol users), or certain geographic areas with a high incidence of oral cancer and precancer.[138]

Classification and staging system
In order to promote uniform reporting of various aspects of leukoplakia, there is a need for a classification and staging system in which the site, the clinical subtype and the histopathological features are taken into account. A proposal for such a classification and staging system has been presented in Table 4.[139] The staging system (Stages I-IV) has not yet been proven to be of value with regard to the management of the patient. A somewhat debatable item that has been included in the staging system is the assumption that there are, indeed, high-risk sites (tongue and floor of the mouth). This may be true in certain parts of the

world, e.g. North America and Europe, but not so or different in other parts, e.g. India.

Table 4: **LSCP**-classification and staging system for oral leukoplakia[139]

1st symbol: **L** = extent of the lesion

- L_0 = no evidence of lesion
- L_1 = lesion < 2 cm
- L_2 = lesion 2-4 cm
- L_3 = lesion > 4 cm
- L_x = not specified

2nd symbol: **S** = site of the lesion

- S_1 = all oral sites, except for the floor of the mouth and the tongue
- S_2 = floor of the mouth and/or tongue
- S_x = not specified

3rd symbol: **C** = clinical aspect

- C_1 = homogeneous
- C_2 = non-homogeneous
- C_x = not specified

4th symbol: **P** = histopathological features of biopsy, if taken

- P_1 = no dysplasia
- P_2 = mild dysplasia
- P_3 = moderate dysplasia
- P_4 = severe dysplasia
- P_x = not specified

Staging is only performed in leukoplakias that have been examined histopathologically

Stage 1: any L, S_1, C_1, P_1, or P_2
Stage 2: any L, S_1, C_2, P_1, or P_2
: any L, S_2, C_1, P_1, or P_2
Stage 3: any L, S_2, C_2, P_1, or P_2
Stage 4: any L, any S, any C, P_3 or P_4

Table 4: LSCP-classification and staging system for oral leukoplakia (cont'd)

General rules of the LSCP system:

(1) If there is doubt concerning the correct L, S, C, or P category to which a particular case should be alloted, then the lower (i.e. less advanced) category should be chosen. This will also be reflected in the stage grouping.

(2) In the case of multiple simultaneous leukoplakias, the lesion with the highest L and/or the highest S category should be classified and the multiplicity of the number of leukoplakias should be indicated in parentheses, e.g. $L_{2(m)}$.

(3) In the case of different clinical types of leukoplakias the highest score of the various leukoplakias should be used.

(4) In the case of multiple biopsies of a single leukoplakia or biopsies taken from multiple leukoplakias the highest pathological score of the various biopsies should be used.

(5) For reporting purposes the oral subsite according to the ICD-DA should be mentioned (World Health Organization, International classification of diseases. Tenth revision. Application to dentistry and stomatology. ICD-DA, Geneva, 1992).

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A PROPOSAL FOR A CLASSIFICATION AND STAGING SYSTEM FOR ORAL LEUKOPLAKIA; A PRELIMINARY STUDY.

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A PROPOSAL FOR A CLASSIFICATION AND STAGING SYSTEM FOR ORAL LEUKOPLAKIA; A PRELIMINARY STUDY.

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Abstract

A classification and staging system for oral leukoplakia is proposed based on the recently revised definition of this premalignant lesion. The initial experiences of this system are described on the basis of 100 patients with oral leukoplakia. The new classification and staging system seems very suitable for characterizing groups of patients with oral leukoplakia. Whether this system is also valuable with regard to guidelines for management of these patients has still to be proven.

Introduction

A classification and staging system has recently been developed for patients with premalignant lesions of the oral mucosa, with particular reference to leukoplakia. Oral leukoplakia has been defined as "a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some leukoplakias are precancerous".[1] A distinction is made between a *provisional* and a *definitive* diagnosis of oral leukoplakia. A provisional diagnosis of oral leukoplakia is made when on clinical examination a lesion cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance. The definitive diagnosis "oral leukoplakia" is made as a result of the identification, and if possible, elimination of suspected aetiological factors and, in the case of persistent lesions, histopathological examination. A white lesion that regresses after the elimination of the possible aetiological factors must be named after the causative factor(s), e.g., frictional lesion, tobacco lesion or candidiasis. A definitive diagnosis must be based on a biopsy. Clinically, leukoplakias are divided into a homogeneous and a non-homogeneous form.[2]

The premalignant potential of oral leukoplakia may be related to aetiological, topographical, clinical or histological characteristics. Presence of symptoms, absence of recognized aetiologic factors, long duration, and a history of previous oral cancer are factors that must be considered in the management of oral leukoplakia, since these features, together with location in so called high-risk sites (floor of the mouth and/or the tongue), a non-homogeneous clinical subtype and the presence of epithelial dysplasia, would appear to be associated with an increased risk of malignant transformation.[3-7] The presence of epithelial dysplasia appears to be the most important indicator of malignant potential.[8]

The new classification system is based on the size of the leukoplakia (L), the site (S), the clinical aspect (C), and the histopathological features (P), if applicable (Table 1). This system can be incorporated into a staging system (Table 2); the latter should only be used for leukoplakias that have been examined histologically.

The purpose of this study is to describe the initial experiences with this new classification and staging system on the basis of 100 patients with oral leukoplakia.

Table 1: Proposal for a classification system for oral leukoplakia.

Provisional (clinical) diagnosis:

1st symbol: **L** = Extent of the leukoplakia

L_0 = no evidence of lesion
L_1 = lesion $\leq$ 2 cm
L_2 = lesion 2 - 4 cm
L_3 = lesion $\geq$ 4 cm
L_X = not specified

2nd symbol: **S** = Site of the leukoplakia

S_1 = all oral sites, except for the floor of the mouth and the tongue
S_2 = floor of the mouth and/or the tongue
S_X = not specified

3rd symbol: **C** = Clinical aspect

C_1 = homogeneous
C_2 = non-homogeneous
C_X = not specified

Definitive (histopathological) diagnosis:

4th symbol: **P** = Histopathological features

P_1 = no dysplasia
P_2 = mild dysplasia
P_3 = moderate dysplasia
P_4 = severe dysplasia
P_X = not specified

Table 2: Proposal for a staging system for oral leukoplakia (only for leukoplakias that have been examined histopathologically).

Stage 1:	any L, S_1, C_1, P_1 or P_2
Stage 2:	any L, S_1, C_2, P_1 or P_2
	any L, S_2, C_1, P_1 or P_2
Stage 3:	any L, S_2, C_2, P_1 or P_2
Stage 4:	any L, any S, any C, P_3 or P_4

General rules of the LSCP system:

1. If there is doubt concerning the correct L, S, C, or P category to which a particular case should be alloted, then the lower (i.e. less advanced) category should be chosen. This will also be reflected in the stage grouping.

2. In case of multiple simultaneous leukoplakias, the leukoplakia with the highest L and/or the highest S category should be classified and the multiplicity of the number of leukoplakias should be indicated in parentheses e.g. $L_{2(m)}$.

3. In case of different clinical types of oral leukoplakia the highest score should be used of the various leukoplakias.

4. In case of multiple biopsies of a single leukoplakia or biopsies taken from multiple leukoplakias the highest pathologic score of the various biopsies should be used.

5. For reporting purposes the oral subsite according to the ICD-DA should be mentioned.

Patients and Methods

For this study 100 consecutive patients with a diagnosis of oral leukoplakia were retrieved retrospectively from the files of the Department of Oral and Maxillofacial Surgery/Oral Pathology of the Free University Hospital in Amsterdam, during the period January 1, 1975 to January 1, 1995. The group of patients consisted of 51 men and 49 women, with a mean age of 55.9 (range: 22 to 82). Patients with oral leukoplakia and a simultaneous squamous cell carcinoma of the oral cavity were not included in this study. The group of 100 patients was divided into two groups registered either as "provisional leukoplakia" (group I) or "definitive leukoplakia" (group II). Group I consisted of 39 patients while group II contained 61 patients.
For various reasons eight patients were excluded from the latter group. The remaining 53 patients were staged. The sites were specified according to the anatomical distribution recommended by the ICD-DA.[9]

Results

Group I consisted of 37 homogeneous (C_1) and 2 non-homogeneous (C_2) leukoplakias. The distribution of the leukoplakias according to the oral subsite and the clinical aspect are shown in Table 3.
Group II consisted of 25 homogeneous (C_1) and 28 non-homogeneous (C_2) leukoplakias. The distribution of the leukoplakias according to stage and subsite is shown in Table 4. Stage 1 consisted of 9 patients, 4 males and 5 females. Histopathological examination of 3 leukoplakias out of 9 in this stage showed mild epithelial dysplasia (P_2).
Stage 2 consisted of 17 patients, 7 males and 10 females. Histopathological examination of 7 leukoplakias showed mild epithelial dysplasia.
Stage 3 consisted of 6 patients, 3 males and 3 females. Histopathological examination of 4 leukoplakias showed mild epithelial dysplasia.
Stage 4 consisted of 21 patients, 13 males and 8 females. Eighteen out of 21 leukoplakias with moderate to severe epithelial dysplasia (stage 4) were clinically diagnosed as non-homogeneous leukoplakias. All but three leukoplakias in this stage, clinically diagnosed as non- homogeneous (C_2), were located in the floor of the mouth or on the tongue.

Table 3: Distribution of 39 leukoplakias in group I (provisional diagnosis) according to the oral subsite and the clinical aspect.

Localisation: Subsites	Clinical aspect		Total
	C_1	C_2	
0. unknown	-	-	-
1. lower lip, vermilion surface	-	-	-
2. upper lip, vermilion surface	-	-	-
3. commissures	5	1	6
4. mucosal surfaces upper and lower lips	-	-	-
5. cheek mucosa	6	-	6
6. retromolar areas	-	-	-
7. bucco-alveolar sulci, upper and lower	-	-	-
8. upper alveolus and gingiva	4	-	4
9. lower alveolus and gingiva	-	1	1
10. hard palate	-	-	-
11. tongue, dorsal surface and lateral borders	7	-	7
12. inferior surface tongue	-	-	-
13. floor of mouth	7	-	7
14. multiple sites	8*	-	8
Total	**37**	**2**	**39**

* In 5 patients a "high-risk" site (floor of mouth and/or tongue) was involved.

Table 4: Distribution of 53 leukoplakias in group II (definitive diagnosis) according to the stage and the oral subsite.

Localisation: Subsites	Group II				Total
	Stage 1	Stage 2	Stage 3	Stage 4	
0. unknown	-	-	-	-	-
1. lower lip, vermilion surface	1	1	-	1	**3**
2. upper lip, vermilion surface	-	-	-	-	-
3. commissures	1	2	-	1	**4**
4. mucosal surfaces upper and lower lips	-	-	-	-	-
5. cheek mucosa	1	-	-	-	**1**
6. retromolar areas	-	-	-	-	-
7. bucco-alveolar sulci, upper and lower	-	-	-	-	-
8. upper alveolus and gingiva	1	1	-	1	**3**
9. lower alveolus and gingiva	2	-	-	-	**2**
10. hard palate	1	-	-	-	**1**
11. tongue, dorsal surface and lateral borders	-	5	2	11	**18**
12. inferior surface tongue	-	1	-	-	**1**
13. floor of mouth	-	5	1	7	**13**
14. multiple sites	2	2	3	-	7
Total	**9**	**17**	**6**	**21**	**53**

Discussion

The classification and staging (LSCP) system has been developed along the lines of the TNM-classification system for cancer. The LSCP system is based on a - provisional - clinical diagnosis (symbols L, S and C) combined with a - definitive - histopathological diagnosis (symbol P). The decision to biopsy a leukoplakic lesion is, apart from the diagnostic expertise of the clinician, in general primarily based on the clinical aspect, in particular a non-homogeneous type, the presence of symptoms and/or the oral subsite. Despite the above-mentioned, two leukoplakias showing a non-homogeneous aspect, and five leukoplakias located at a high risk site (i.e. floor

of mouth and/or the tongue) in group I (Table 3) had not been biopsied.

The stage grouping for oral leukoplakia includes the size, the site, the clinical aspect, and the histopathological features of the leukoplakia. The stages are based on the assumption that the risk factors included have a cumulative predictive effect on the premalignant potential of oral leukoplakia. However, the size of the leukoplakia (symbol L) does not influence the staging of the lesion and could, in fact, be dropped from the stage grouping system. In this study the extent of the leukoplakia could not be specified (Lx) in a relatively large number of patients; this can be largely explained by the retrospective nature of the study.

The classification and staging system for oral leukoplakia is a "shorthand" method to describe the most essential characteristics of this premalignant lesion, and can be helpful in characterizing groups of patients affected by oral leukoplakia (see Tables 3 and 4), and in supporting the decision on whether or not active treatment should be instituted. The indication for active treatment of oral leukoplakia appears to depend largely on the histopathological findings of a biopsy. In the presence of moderate to severe epithelial dysplasia (stage 4) active treatment should be instituted.[5,10] In case of mild or in the absence of epithelial dysplasia the decision to treat may be influenced by the site or the clinical aspect of the lesion (stage 1, 2 and 3). In general, treatment is recommended for leukoplakias located in "high-risk" sites, irrespective of the degree of epithelial dysplasia. The significance of the present staging system for the management of and prognosis for patients with oral leukoplakia requires further investigation.

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- Chapter 4 -

PREVALENCE STUDY OF ORAL WHITE LESIONS WITH SPECIAL REFERENCE TO A NEW DEFINITION OF ORAL LEUKOPLAKIA

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Abstract

In this survey the experiences with and implications of a revised definition of oral leukoplakia are described. One of the new aspects of the revised definition is the distinction between a provisional, clinical diagnosis and a definitive one for which histopathological examination is required. A prevalence study of white lesions of the oral mucosa among a selected population of 1000 consecutive patients from The Netherlands showed a prevalence of a provisional and a definitive diagnosis of oral leukoplakia of 0.6 and 0.2 %, respectively. For a uniform reporting, a recently proposed classification and staging system has been used to stage leukoplakias with a definitive diagnosis. The use of the revised definition of oral leukoplakia, as well as the classification and staging system, seem very suitable for epidemiologic studies.

Introduction

In a publication by the WHO in 1978, oral leukoplakia was defined as "A white patch or plaque that cannot be characterized, clinically or pathologically, as any other disease".[1] It was emphasized that the term leukoplakia should only be used in a clinically descriptive way and that it should carry no histologic connotation, which means that the use of the term is unrelated to the absence or presence of epithelial dysplasia. At an international seminar on oral leukoplakia in 1983, it was suggested that the term leukoplakia should be avoided in the case of known aetiology other than the use of tobacco.[2]

In 1994, an international working group on oral leukoplakia has rephrased the definition as "A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakias will transform into cancer".[3] Furthermore, a distinction is made between a provisional (clinical) and a definitive diagnosis of oral leukoplakia. The definitive diagnosis of oral leukoplakia is a result of the identification and, if possible, elimination of suspected aetiological factors and, in the case of persistent lesions, - more than 2 - 4 weeks -, histopathological examination to rule out any other definable lesion and to determine the degree of epithelial dysplasia, if present.

The purpose of this study was to define the prevalence of oral white lesions among a selected population of 1000 consecutive patients from a department of Oral and Maxillofacial Surgery in The Netherlands, with special reference to the use of a new definition of oral leukoplakia.

Materials and Methods

For this study, 1000 consecutive patients who visited the Department of Oral and Maxillofacial Surgery at the Free University Hospital in Amsterdam, were examined as part of a routine oral examination procedure in the period April 1993 - July 1994. Patients who were specifically referred for a white oral mucosal lesion were not included in this study.

The group of 1000 patients consisted of 472 men (47.2%) and 528 women (52.8%), with a mean age of 35 years, both for men and women (range 13 - 93 years). The sex and age distribution are shown in Figure 1. Possible smoking and alcohol habits were recorded (see Table 1). A tobacco and/or alcohol user was defined,respectively, as any person who smoked at least five cigarettes a day and/or drank at least two units of alcohol a day.

Apart from leukoplakia, candidiasis, cheek and lip biting, frictional white lesions, geographic tongue, lesion associated with a dental restoration, leukoedema, leukokeratosis nicotina palati, and lichen planus were considered as target lesions.

Table 1: Distribution of tobacco and alcohol habits among 1000 patients.

Gender	Number of patients	Habits		
		tobacco	alcohol	tobacco and alcohol
Men	472 (47.2%)	216 (45.8%)	115 (24.4%)	77 (14.2%)
Women	528 (52.8%)	195 (36.9%)	39 (7.4%)	22 (4.2%)
Total	**1000 (100%)**	**411 (41.1%)**	**154 (15.4%)**	**99 (9.9%)**

The diagnosis of oral leukoplakia was based on the criteria as provided by Axell et al.[2], retrospectively adjusted according to the new definition as mentioned in the introduction, including the distinction between a provisional and a definitive diagnosis of oral leukoplakia.[3] Clinically, a distinction was made between a homogeneous and a non-homogeneous leukoplakia.[2] Leukoplakias with a definitive diagnosis have been staged according to a recently proposed classification and staging system.[4]
The diagnosis of candidiasis, cheek and lip biting, leukoedema, leukokeratosis nicotina palati, and lichen planus were based on criteria as provided by the WHO.[1] The diagnostic criteria for geographic tongue were based on the definition used by Axell.[5] A lesion associated with a dental restoration was defined as "A lesion with whitish, reddish or whitish-reddish changes of the oral mucosa, occasionally with a lichenoid appearance, with a clear anatomical relation to an amalgam filling".[6] White lesions for which a mechanical factor could be disclosed were diagnosed as frictional lesion.
The localisation of the lesions was specified according to the anatomical distribution recommended by the ICD-DA.[7] Color photographs were taken of all lesions that were provisionally diagnosed as leukoplakia. The management was directed towards the elimination of possible aetiological factors. Biopsies were only taken in selected cases.

Results

The prevalence rates of the target lesions are summarized in Table 2. In six cases out of 1000 patients a provisional diagnosis of oral leukoplakia was made, resulting in a prevalence rate of 0.6%. This group of six patients contained three men and three women, with a mean age of 39 years (range 22 to 55 years). All of these patients were regular smokers. In two out of the six cases, both women, a definitive diagnosis of oral leukoplakia was made based on exclusion of possible aetiological factors and histopathological examination, resulting in a prevalence rate of a definitive diagnosis of oral leukoplakia of 0.2%. The distribution of the six patients with a provisional

and/or definitive diagnosis of oral leukoplakia according to the site of the lesion, the classification and stage is shown in Table 3.

Table 2: Prevalence rates of the target lesions in the group of 1000 patients according to gender.

Lesion	n		prevalence (%)
	M	F	
Candidiasis	9	6	3	**0.9**
Cheek biting	23	8	15	**2.3**
Frictional lesion	25	19	6	**2.5**
Geographic tongue	23	12	11	**2.3**
Lesion assoc. with dental restoration	2	1	1	**0.2**
Leukoedema	30	21	9	**3.0**
Leukokeratosis nicotina palati	10	8	2	**1.0**
Leukoplakia	6	3	3	**0.6**
Lichen planus	6	4	2	**0.6**
Total	**134**	**82**	**52**	**13.4**

M = Male; F = Female

Tabel 3 : Distribution of 6 patients with a provisional and/or definitive diagnosis of oral leukoplakia according to site, classification and stage.

Patient	Diagnosis leukoplakia		Site of leukoplakia	Classification	Stage
	Provisional	Definitive			
1.F;22yr	+	-	floor of mouth	$L_1S_2C_1$	-
2.M;28yr	+	-	floor of mouth	$L_1S_2C_1$	-
3.M;38yr	+	-	lateral border of the tongue	$L_1S_2C_1$	-
4.M;45yr	+	-	commissure	$L_1S_1C_2$	-
5.F;48yr	+	+	floor of mouth	$L_1S_2C_1P_1$	2
6.F;55yr	+	+	lateral border of the tongue	$L_1S_2C_1P_2$	2

* F = Female; M = Male

** LSCP = Symbols used in the classification system for oral leukoplakia, in which L,S,C, and P respectively stands for size of Leukoplakia (L), Site (S), Clinical aspect (C), and Pathology (P).

Discussion

The results of this prevalence study are derived from a selected and relatively small population, which means that comparison with other epidemiologic studies should be looked upon with some reservation.

The low prevalence rate in the present study may be due to the fact that the majority of the examined patients were in the age group of twenty to twenty-nine years (Figure 1), while the onset of oral leukoplakia generally takes place after the age of 40 years.[8] Another explanation for the low percentage in the present study may be attributed to the exclusion of patients from this study who were referred for diagnosis of a white mucosal lesion.

In Table 4 epidemiological data on the prevalence of oral leukoplakia as retrieved from the literature, are given.[5,9-24] In several studies the taking of biopsies has not been reported. Therefore, it is not known whether the diagnosis was based on clinical grounds alone or included a histological examination. This may make the comparison of these prevalence figures with the present study problematical. In the study of Bouquot and Gorlin, histopathological examination revealed, in 22 cases out of 682 clinically diagnosed leukoplakias, a squamous cell carcinoma.[19] Based on histopathological grounds and according to the definition of oral leukoplakia in that study, these lesions should have been excluded from the diagnosis leukoplakia and be ranked as "other definable lesions".

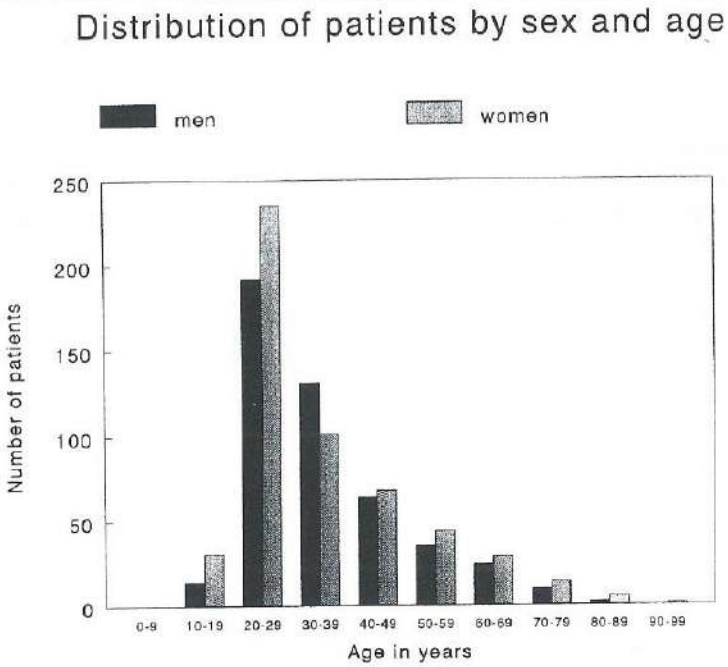

Figure 1: Age and sex distribution of 1000 patients.

The target lesions other than oral leukoplakia in the present study are considered to be distinct clinical entities. In the new definition, these lesions are ranked as "other definable lesions". A number of such cases cannot always be classified as such at the first oral examination and may than provisionally be diagnosed as leukoplakia. Since the diagnosis of white oral mucosal lesions in epidemiologic studies are usually based on a single oral examination, an erroneous diagnosis of leukoplakia may result. From the literature, it is known that some white lesions in persons using tobacco may be reversible after cessation of the smoking habit.[28,29] Such lesions can provisionally be diagnosed as leukoplakia, and, if they regress, could be named "tobacco-associated lesion". If the lesion persists after cessation of the smoking habit or when the patient has continued to smoke, the provisional diagnosis of oral leukoplakia remains unchanged and should preferably be transformed into a definitive diagnosis by the taking of a biopsy.

In the present study, no causative factors could be detected in the provisionally diagnosed leukoplakias. Only two of these lesions had been biopsied. According to the revised definition of leukoplakia, a biopsy should preferably be taken in all lesions that persist after a waiting period of two to four weeks.

For a uniform documentation and reporting, a recently proposed classification and

staging system based on the revised definition of oral leukoplakia has been used (see Table 3). The symbols used in this system represent clinical and histopathological features of oral leukoplakia, that are supposed to have a predictive value with regard to the malignant transformation. Only the two cases with a definitive diagnosis of oral leukoplakia were eligible for staging. We recommend to clearly state in papers on oral leukoplakia whether the diagnosis is a clinical, provisional or a definitive one.

Table 4: Studies on the prevalence of oral leukoplakia

Author	Year	Country	No. examined persons	Age	Character	No. leukoplakias	No. biopsies	Definition	Prevalence (%)
Pindborg et al.[9-11]	1965-1966	India	30 000	N.R.	Rural/Urban	150-328	N.R.	Pindborg 1963[25]	1.5 - 3.3
Zachariah et al.[12]	1966	India	5 000	N.R.	Rural	118	N.R.	Pindborg 1963	2.4
Pindborg et al.[13]	1968	New Guinea	1 266	> 20	Rural	56	16	Pindborg 1963	4.6
Mehta et al.[14]	1969	India	50 915	> 15	Rural	881	723	Pindborg 1963	1.7
Gangadarhan & Paymaster[15]	1971	India	203 249	All	Urban	1422	N.R.	Pindborg 1963	0.7
Mehta et al.[16]	1972	India	101 761	> 15	Rural	685	N.R.	Pindborg 1963	0.7
Axell T.[5]	1976	Sweden	20 333	> 15	Urban/Suburban/Rural	717	N.R.	Silverman 1963[26]	3.6
Lay et al.[17]	1982	Burma	6 000	> 15	Rural	101	N.R.	WHO 1980*[27]	1.7
Rodriquez et al.[18]	1983	Cuba	749	20-75	Urban workers	16	N.R.	WHO 1978[1]	2.1
Bouquot & Gorlin[19]	1986	USA	23 616	> 35	Rural/Urban	682	176	WHO 1978	2.9
Reichart et al.[20]	1987	Thailand	1 866	All	Rural	21	N.R.	WHO 1978	1.1
Hogewind & van der Waal[21]	1988	The Netherlands	1 000	All	Urban	14	3	Seminar 1983[2]	1.4
Ikeda et al.[22]	1991	Japan	3 131	All	Urban	77	N.R.	Seminar 1983	2.5
Banoczy et al.[23]	1991	Hungary	7 820	All	Rural	104	N.R.	Seminar 1983	1.3
Ikeda et al.[24]	1995	Cambodia	1 319	> 15	Urban	14	N.R.	WHO 1980*	1.1

(N.R. = not reported;* = same definition as WHO 1978).

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- Chapter 5 -

MALIGNANT TRANSFORMATION OF ORAL LEUKOPLAKIA;

A follow-up study of a hospital based population of 166 patients with oral leukoplakia from The Netherlands

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Abstract
A follow-up study of a hospital based population of 166 patients with oral leukoplakia revealed a 2.9% annual malignant transformation rate. The median follow-up period was 29 months. Parameters associated with an increased risk of malignant transformation were female gender ($p < 0.025$), absence of smoking habits in women ($p < 0.05$), and a non-homogeneous clinical aspect ($p= 0.01$).
For uniform reporting, a recently proposed classification and staging system has been used. Leukoplakias in stage IV, consisting of lesions with moderate or severe epithelial dysplasia, were associated with an increased risk of malignant transformation ($p < 0.01$). There were no oral subsites associated with an increased risk. Patients who had any form of intervention did not have a statistically significantly lower chance for malignant transformation, than patients who were kept under surveillance without intervention.

Introduction
Oral leukoplakia is a precancerous or potentially malignant lesion, which means that in this morphologically altered tissue cancer is more likely to occur than its apparently normal counterpart.[1] Oral leukoplakia is defined as "A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion".[2] The frequency of malignant transformation in oral leukoplakia varies between 0 and 20% during an observation period of 1 to 30 years.[3-9] In general, it is more or less accepted as an overall statement that approximately 5 % of all leukoplakias will transform into cancer in an average period of 5 years.
In the present follow-up study of 166 patients with oral leukoplakia the figures on malignant transformation are presented. Parameters indicative for malignant transformation of oral leukoplakia such as epidemiological and aetiological factors, and clinical and histopathological features are described.

Patients and Methods
Patients In the period 1973 -1997, 263 patients were referred to the Department of Oral and Maxillofacial Surgery at the Academic Hospital Vrije Universiteit with an initial diagnosis of oral leukoplakia. No reliable information was available about duration of the presence of the leukoplakia. The clinical diagnosis of oral leukoplakia was based on the criteria as provided by Axell et al.[10], adjusted according to the most recent definition.[2] Clinically, a distinction was made between a homogeneous and a non-homogeneous leukoplakia; the latter includes erythroleukoplakias, nodular, exophytic, and proliferative verrucous types.[2] In case a biopsy was taken the term leukoplakia was replaced by the histopathological diagnosis of a dysplastic or a non-dysplastic lesion.[11] Patients in whom the leukoplakia was biopsied, were staged according to a recently proposed classification and staging system.[12] The taking and site of the biopsies depended on clinical judgement, and findings such as a red or verrucous component, ulceration or induration on palpation, and the presence of symptoms.
For the purpose of this study seven patients were excluded because of a history of a previous neoplasm in the head and neck region. Twenty-seven patients were excluded because the lesion proved to be "another definable lesion" on histopathological examination (6 squamous cell carcinomas, 1 carcinoma-in-situ, 17 verrucous carcinomas, 3 hyperplastic candidiasis). There remained a total of 229 patients.
Malignant transformation To evaluate malignant transformation, the group of 229 patients was restricted to those with a minimum follow-up of six months. A total of 166 patients fulfilled this criterion: 76 men and 90 women (mean age: 57 years (range 23 - 91 years)) (Figure 1). Tobacco and alcohol habits are summarized in Table 1.

The localisation of the leukoplakias was specified according to the anatomical distribution recommended by the ICD-DA (Table 2).[13] The clinical subtype and histopathological diagnosis are shown in Table 3.

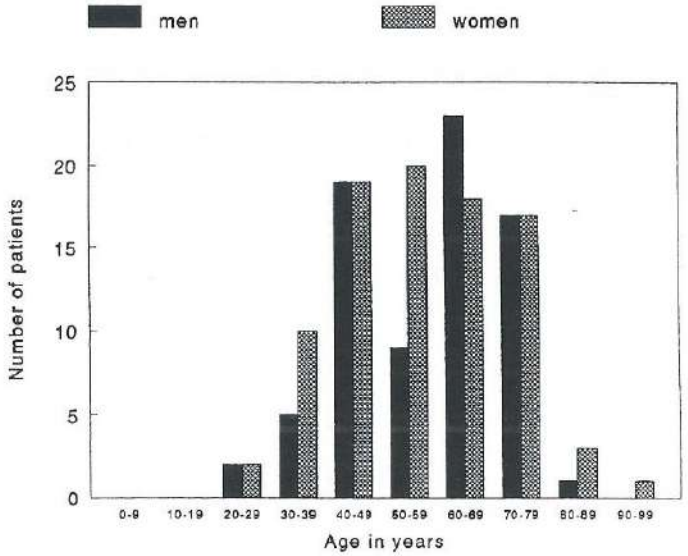

Figure 1: Distribution of 166 patients with oral leukoplakia by gender and age.

Table 1: Distribution of tobacco and alcohol (in units/day) habits among 166 patients with oral leukoplakia according to gender.

Gender	Patients	Habits					
		Tobacco			Alcohol		
		Unknown	Non-smokers	Smokers	Unknown	< 2 U/day	> 2 U/day
Men	76	5	25	46	23	22	31
Women	90	10	33	47	16	63	11
Total	**166**	**15**	**58**	**93**	**39**	**85**	**42**

Initial and follow-up treatment modalities are summarized in Table 4 and 5, respectively. Eighty-seven patients underwent active treatment after the first visit or shortly there-after or during follow-up. Two patients refused active treatment.

Follow-up visits were scheduled at 3, 6 or 12 months intervals (based upon clinical or histopathological aspects), until either lost to follow-up or death. The follow-up period ranged from 6 - 209 months with a median of 29 months. The other endpoint of the study was a diagnosis of squamous cell carcinoma at the site of the leukoplakia or elsewhere in the oral cavity. The diagnosis of squamous cell carcinoma was based on histopathological examination of a representative incisional or excisional specimen.

Statistics Minimum, maximum, mean and median values of continuous variables were calculated. Relevant data were cross-tabulated and odds ratios were tested with the Chi-square test. The results were considered statistically significant if the p-value was less than 0.05. The interval between inclusion and either end of follow-up or malignant transformation was expressed in months. Of these data, a follow-up curve was plotted according to the Kaplan-Meier method. The same was done for the group who had any form of intervention (n = 87), and the group who had not (n = 79).

Table 2: Site distribution of 166 patients with leukoplakia.

Oral subsite	Number of patients
External lower lip (vermilion border)	6
Commissures	13
Cheek mucosa	13
Upper alveolus and gingiva	14
Lower alveolus and gingiva	6
Hard palate	3
Tongue (dorsal and lateral surfaces)	54
Floor of mouth	32
Multiple anatomical sites	25*
Total	**166**

* In 15 patients the tongue or floor of mouth was involved.

Table 3: Clinical subtypes and histopathological diagnosis in 166 patients with oral leukoplakia.

Clinical subtype	Histopathological diagnosis						Total
	Non-dysplastic lesion	Dysplastic lesion			Not-specified	No biopsy taken	
		Mild	Moderate	Severe			
Homogeneous	35	13	8	2	2	39	99
Non-homogeneous	12	7	16	16	2	4	57
Not specified	6	-	2	1	-	1	10
Total	53	20	26	19	4	44	166

Table 4: Treatment modalities instituted after first visit (or shortly thereafter) in 166 patients with oral leukoplakia.

Initial treatment	Number of patients
Excision	37
Laser	5
Cryosurgery	5
Retinoids	1
Surveillance ("Wait & See")	118
Total	**166**

Table 5: Treatment modalities in the follow-up of 118 "Surveillance" patients with oral leukoplakia.

Treatment during follow-up	Number of patients
Excision	28
Laser	5
Cryosurgery	5
Retinoids	1
Surveillance ("Wait & See")	77
Refusal of active treatment	2
Total	**118**

Results

Twenty (12.0%) out of 166 patients, 16 women and 4 men, developed a squamous cell carcinoma during follow-up. The event occurred after a median of 32.0 months (range: 6-201 months). The estimated time for this event to occur was 200.8 months in 50 % of the patients (Figure 2). The calculated malignant transformation rate was thus 2.9% per year.

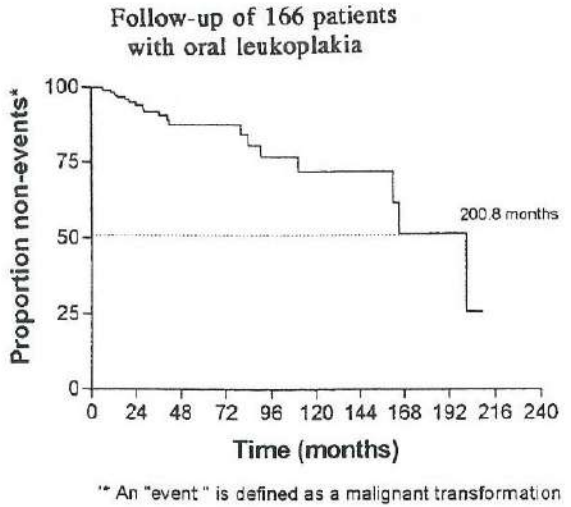

Figure 2: Follow-up of 166 patients with oral leukoplakia (50 %) of patients will have an 'event' after 200.8 months, resulting in a malignant transformation rate of 2.9 % per year).

The female preponderance in the group of malignant transformation is statistically significant ($p < 0.025$). The mean age at the first visit of 67.1 years (range: 44 - 87) in the group who underwent malignant transformation appeared to be significantly higher than the mean age of 55.8 years (range: 23 - 91) in the group who did not ($p < 0.001$). The mean age at the time the carcinoma was diagnosed, was 71.4 years (range: 46.3 - 90.8 yrs).
Women without smoking habits were significantly higher at risk for malignant transformation than women who smoked ($p < 0.05$). No significant relationship was found with respect to smoking habits in men. There was no correlation between alcohol habits in men and women with respect to malignant transformation.
The site distribution of the leukoplakias and carcinomas is listed in Table 6. The subsite of the leukoplakia was not a risk factor for malignant transformation ($p > 0.05$).

Table 6: Site distribution of 166 patients with oral leukoplakia and number of patients with malignant transformation.

Oral subsite	No. of patients	No. of patients with malignant transformation
Tongue and floor of mouth, including multiple sites in which the tongue and floor of mouth were affected.	101	15
Other oral subsites, including multiple sites in which the tongue and floor of mouth were **not** affected	65	5
Total	**166**	**20**

No significant difference between so-called high-risk sites, tongue and floor of mouth, compared to other oral subsites ($p > 0.05$)

The chance of malignant transformation was statistically significantly higher ($p = 0.01$) for leukoplakias with a non-homogeneous clinical aspect. In Table 7 the distribution of 109 patients eligible for staging, subdivided into patients with and without malignant transformation, is summarized. Leukoplakias staged IV,

consisting of moderate or severe epithelial dysplasia, had a significantly higher risk to develop a carcinoma than leukoplakias of a lower stage ($p < 0.01$).

Table 7: Staging of 109 patients with oral leukoplakia sudivided in patients who underwent malignant transformation, and patients who did not.

STAGE	No malignant transformation	Malignant transformation	Total
I.	17	-	**17**
II.	35	2	**37**
III.	7	1	**8**
IV.	36	11	**47**
Total	**95**	**14**	**109**

Out of 8 patients, treated surgically for their leukoplakia before the carcinoma developed, 7 had recurrent leukoplakia. In one patient, treated with retinoids, at the outset regression was noted. In 9 patients a "wait & see" policy was followed. Two patients refused any kind of active treatment of the leukoplakia.
Patients who underwent any form of active treatment ($n = 87$) did not have a statistically significantly lower chance for malignant transformation ($p = 0.18$), than patients who were only kept under surveillance without intervention ($n = 79$) (Figure 3).

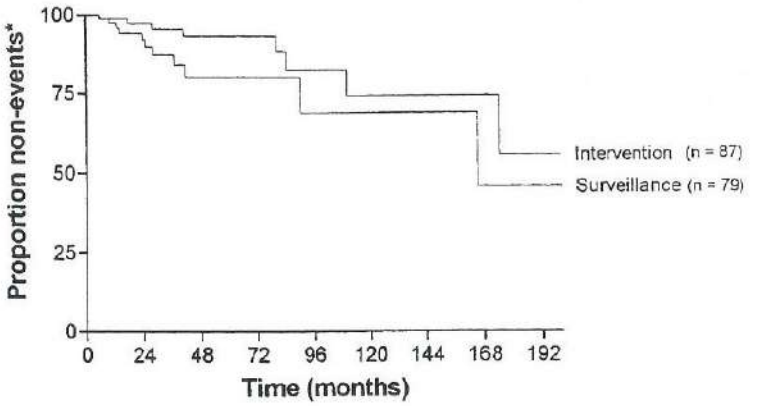

Figure 3: Follow-up of 166 patients with oral leukoplakia, of whom 87 had active treatment (intervention), and 79 had not (surveillance) ($p > 0.05$).

Discussion

The calculated annual malignant transformation rate of 2.9 % during a median follow-up period of 29 months is in accordance with transformation rates known in the literature.[4-9,14,15] However, due to the retrospective character of the study the total number of patients with leukoplakia might have been underreported, resulting in a lower rate of malignant transformation. Furthermore, the group of patients is derived from a selected population, whereas malignant transformation rates derived from unselected villagers appear to be much lower.[16-18] In Figure 2 it is demonstrated that the longer the follow-up period of the persons at risk, the higher the number of malignant transformed leukoplakias. This relationship has also been shown in other studies.[8,9,19]

In the present study the gender distribution of the total leukoplakia group shows a small female preponderance, whereas reported rates generally show a higher involvement of the male sex.[20] The female preponderance in the group with malignant transformation is statistically significant ($p < 0.025$). Others have reported this unexplained predilection for the female gender as well.[21,22]

The increased risk of malignant transformation of oral leukoplakia in women without tobacco habits (often referred to as idiopathic leukoplakia), as shown in the present study, gives support to the findings of previous studies as well.[9,22] It remains unclear why the absence tobacco habits is associated with an increased risk of malignant transformation in women only.

Several studies have demonstrated that the buccal mucosa is the most frequently affected site of oral leukoplakia, whereas the tongue and floor of mouth are affected in only a small percentage.[19,23] However, in the present study the most frequently affected sites were the lateral borders of the tongue and the floor of the mouth (60.8 % of the cases). This site distribution may be explained by a referral and/or population bias.

In several studies it has been shown, that most carcinomas develop from leukoplakias on the lateral borders of the tongue or in the floor of mouth, being referred to as "high-risk" sites.[23-26] However, in the present study there were no subsites significantly associated with an increased risk. Furthermore, in two patients the cancer developed at another site than the initial site of the leukoplakia, which may support the concept of "field cancerization".

The presence of epithelial dysplasia seems to correlate with a non-homogeneous clinical aspect and vice versa (Table 3). Table 3, however, demonstrates that clinically homogeneous leukoplakias may also exhibit distinct features of epithelial dysplasia. No reliable information was available in the records why no biopsy was taken in 44 patients. In 2 of 39 patients with homogeneous leukoplakias, in whom no biopsy was taken, a squamous cell carcinoma has developed. Therefore, we recommend to take a biopsy in all clinical subtypes of leukoplakia, also in view of subjectivity with regard to this subtyping.[11]

In six patients with carcinomatous changes, no epithelial dysplasia was present in the initial biopsy. Indeed, as shown by others as well, malignant transformation may take place in non-dysplastic lesions.[9,27,28] At the same time, one should realize that the grading of epithelial dysplasia carries some subjectivity.[29,30]

Moderate and severe dysplastic lesions staged IV, had a significantly higher risk to develop a carcinoma than leukoplakias of a lower stage. As epithelial dysplasia appears to be one of the most important indicators of malignant potential,[28] and stage IV is represented by moderate to severe epithelial dysplasia this, in fact explains the difference.

In eight patients, who had been treated surgically, 7 had recurrent leukoplakia before the cancer developed. Recurrence rates for surgical excision vary from 20 to 35 per cent.[7,31,32] It has been questioned by Einhorn and Wersall, whether active treatment of the leukoplakia would truly prevent the patient of developing cancer. In their study no reduction in the incidence of cancer could be shown in patients surgically treated for their leukoplakia.[33] The present study gives support to their findings.

Conclusions

The importance of certain said risk factors, such as oral subsite and clinical aspect, associated with an increased chance of malignant transformation of oral leukoplakia should not be overestimated. Apparently, clinically innoceous leukoplakias may transform into cancer, irrespective of the oral subsite. Staging may have predictive value for malignant transformation for groups of patients, but should be interpreted carefully with regard to the individual patient.

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- Chapter 6 -

CONCOMITANT LEUKOPLAKIA IN PATIENTS WITH ORAL SQUAMOUS CELL CARCINOMA

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Abstract

Objective: There is an ongoing debate on the prevalence of premalignant lesions, in particular leukoplakia, at the time of diagnosis of an oral squamous cell carcinoma (OSCC). The aim of the present study was to determine the presence of concomitant leukoplakia in 100 patients with OSCC, and to evaluate possible differences in clinical and histopathological parameters of the OSCC between those with or without concomitant leukoplakia.

Patients & Methods: Hundred consecutive patients, 61 men and 39 women, with a histologically proven OSCC were screened on the presence of leukoplakia. Four groups were distinguished: I) leukoplakia adjacent to the OSCC, II) combination of leukoplakia adjacent to the OSCC, and leukoplakia at another oral site, III) leukoplakia present at another oral site, but not adjacent to the OSCC, IV) no leukoplakia present.

Results: In 47 (47 %) patients with OSCC the presence of concomitant leukoplakia was observed. Thirty-six (36 %) patients had a leukoplakia adjacent to the OSCC (group I and II), of which 8 (8 %) patients (group II) also had a leukoplakia present at another oral site. Eleven (11 %) patients (group III) had no leukoplakia adjacent to the OSCC, but a leukoplakia present at another oral site. Fifty-three (53 %) patients (group IV) with OSCC had no concomitant leukoplakia present.No differences were noted between men and women, nor was there any preference for an oral subsite with regard to the carcinoma. There were no statistically significant differences in clinical and histopathological presentation of OSCC's between those with or without concomitant leukoplakia.

Conclusion: Almost fifty per cent of oral squamous cell carcinomas is presumably associated with or preceded by leukoplakia. Early detection and active management of patients with oral leukoplakia may prevent the true development of a number of oral squamous cell carcinomas.

Introduction

There is an ongoing debate on the prevalence rate of leukoplakia in patients presenting with oral squamous cell carcinoma, the reported percentages ranging from 11 % to approximately 60 % (Table 1).[1-10]

The purpose of the present study was to determine the concomitant presence of oral leukoplakia in 100 consecutive patients with a histologically proven squamous cell carcinoma of the oral cavity, and to evaluate possible differences in clinical and histopathological presentation between OSCC's with or without concomitant leukoplakia.

Table 1: Squamous cell carcinoma of the oral cavity associated with leukoplakia.

Author(s)	Year	Country	No. of patients with carcinoma	% With leukoplakia
Present study	1999	Netherlands	100	47.0
Scheifele & Reichart[1]	1998	Germany	101	15.8
Pinholt et al.[2]	1997	Denmark	100	33.0
Bouquot et al.[3]	1987	U.S.A.	61	36.1
Jussawalla & Bhansali[4]	1969	India	12,450	32.0
Chierici et al.[5]	1968	U.S.A.	874	15.0
Gardner[6]	1965	U.S.A.	890	18.0
Silverman[7]	1963	U.S.A.	834	19.0
Paymaster[8]	1962	India	10,580	32.0
Haym[9]	1961	Germany	62	11.0
Weisberger[10]	1957	U.S.A.	275	60.0

Patients and Methods

Patients: In the present study 100 consecutive patients with a histologically proven squamous cell carcinoma of the oral cavity (OSCC), referred to the Department of Oral and Maxillofacial Surgery of our hospital, were examined for the presence of concomitant leukoplakia. All patients were seen in the period March 1993 – April 1995. The group of 100 patients with OSCC consisted of 61 men and 39 women with a mean age of 62 years (range 20 to 104).

Methods: The clinical diagnosis of oral leukoplakia was defined as ' a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion'.[11] Deliberately, no attempt was made in this study to distinguish several clinical subtypes of leukoplakia.

The oral (sub)sites (lip vermilion included) of the tumor and the leukoplakia were specified according to the criteria of the International Union Against Cancer.[12]
The localisation of the leukoplakia in relation to the tumor was divided into four groups: *Group I*) leukoplakia adjacent to the OSCC ('Adjacent'); *Group II*) combination of leukoplakia adjacent to the OSCC, and leukoplakia at another oral subsite ('Adjacent + remote'); *Group III*) leukoplakia present at another oral subsite, but not adjacent to the OSCC ('Remote'); *Group IV*) no leukoplakia present ('None'). Any leukoplakia that was judged to be part of the tumor or located in the same oral subsite was scored as "adjacent". All other leukoplakias were scored as "remote".
Age, tobacco and alcohol habits were recorded. Tobacco usage was divided into non-smokers, incidental smokers (1 to 10 cigarettes per day), moderate smokers (10 to 20 cigarettes per day) and heavy smokers (more than 20 cigarettes per day). The intake of alcohol consumptions was divided into non-drinkers, incidental drinkers (1 to 2 units per day), moderate drinkers (2 to 4 units per day) and heavy drinkers (more than 4 units per day). One unit contains approximately 10 g of alcohol.[13] The tobacco and alcohol habits are summarised in Table 2.
Eighty-eight (88 %) patients underwent surgical excision, 42 (48 %) received postoperative radiotherapy. Three (3 %) patients were only irradiated. Nine (9 %) patients were treated palliatively or refused any kind of treatment. Of the patients treated surgically 50 (57 %) also underwent a neck dissection.
Histopathological data with respect to the degree of differentiation of the OSCC were obtained from the histological report of the operation specimen or the biopsy specimen, available of 88 and 12 patients, respectively. The OSCC's were classified as well, moderately, or poorly differentiated. Histopathological data with respect to lymphatic, vascular, or perineural spread were obtained from the histological reports of the 88 surgically treated patients. For uniform reporting the TNM classification and staging system for malignant tumors was used.[12]
Statistics: Relevant data were cross-tabulated and odds ratios were tested with the Chi-square test. The results were considered statistically significant if the p-value was less than 0.05.

Table 2: Distribution of tobacco and alcohol habits in 100 patients with oral squamous cell carcinoma according to gender.

Gender	Tobacco (%)					
	Unknown	**Not at all**	**Incidental**	**Moderate**	**Heavy**	**Total**
Men	1 (1.6)	13 (21.3)	4 (6.6)	16 (26.2)	27 (44.3)	**61 (61.0)**
Women	1 (2.6)	17 (43.6)	3 (7.7)	5 (12.8)	13 (33.3)	**39 (39.0)**
Total	2 (2.0)	30 (30.0)	7 (7.0)	21 (21.0)	40 (40.0)	**100 (100)**
	Alcohol (%)					
Men	1 (1.6)	2 (3.3)	17 (27.9)	21 (34.4)	20 (32.8)	**61 (61.0)**
Women	1 (2.6)	7 (17.9)	14 (35.9)	12 (30.8)	5 (12.8)	**39 (39.0)**
Total	**2 (2.0)**	**9 (9.0)**	**31 (31.0)**	**33 (33.0)**	**25 (25.0)**	**100 (100)**

Results

In 47 (47 %) patients with OSCC the presence of concomitant leukoplakia was observed. Thirty-six (36%) patients had leukoplakia adjacent to the OSCC (group I and II), of whom 8 (8%) patients (group II) also had a leukoplakia present at another oral site. Eleven (11%) patients (group III) had no leukoplakia adjacent to the OSCC, but at another oral site. Fifty-three (53%) patients (group IV) with OSCC had no concomitant leukoplakia.
There was no statistically significant difference between men and women, with respect to the concomitant presence or absence of leukoplakia (Table 3). The majority of the OSCC's was located on the lateral borders of the tongue, and floor of mouth (Table 4). The presence or absence of oral leukoplakia was not related to a specific site of the OSCC. There were no statistically significant differences in the presence or absence of concomitant leukoplakia between smokers and non-smokers, nor when subdivided according to gender.
Histologically, there were no statistically significant differences in the grade of differentiation between OSCC's with or without leukoplakia. Histopathological examination of the 88 surgically treated patients showed significantly higher vascular spread in patients without concomitant leukoplakia than in patients with concomitant leukoplakia ($p < 0.05$). However, after correction for TNM stage, this feature was non-contributory. No relation was found with respect to lymphatic and /or perineural spread of the tumor with respect to the presence or absence of concomitant leukoplakia.

Stage grouping did not show statistically significant differences between the OSCC's with or without leukoplakia (Table 5).

Table 3: Distribution of oral squamous cell carcinomas (OSCC) with and without concomitant leukoplakia according to gender ($p>0.05$).

Gender	OSCC with leukoplakia (%)	OSCC without leukoplakia (%)	Total (%)
Men	32 (52.5)	29 (47.5)	**61 (61.0)**
Women	15 (38.5)	24 (61.5)	**39 (39.0)**
Total	**47 (47.0)**	**53 (53.0)**	**100 (100)**

Table 4: Site distribution of oral squamous cell carcinoma and subdivided into OSCC with concomitant leukoplakia and without concomitant leukoplakia.

Localisation: subsites	No. of patients (%)	With leukoplakia (%)	Without leukoplakia (%)
Lower lip	5 (5.0)	2 (4.3)	3 (5.7)
Cheek mucosa	7 (7.0)	4 (8.5)	3 (5.7)
Retromolar area	3 (3.0)	1 (2.1)	2 (3.8)
Upper alveolus/gingiva	7 (7.0)	2 (4.3)	5 (9.4)
Lower alveolus/gingiva	3 (3.0)	2 (4.3)	1 (1.9)
Hard palate	3 (3.0)	1 (2.1)	2 (3.8)
Tongue, lateral borders	31 (31.0)	13 (27.7)	18 (34.0)
Floor of mouth	35 (35.0)	18 (38.3)	17 (32.1)
Multiple sites	6 (6.0)	4 (8.5)	2 (3.8)
Total	**100 (100)**	**47 (47.0)**	**53 (53.0)**

Table 5: Stage grouping of oral squamous cell carcinoma with respect to presence or absence of concomitant oral leukoplakia.

Stage	With leukoplakia (%)	Without leukoplakia (%)	Total (%)
I	10 (52.6)	9 (47.4)	**19 (19.0)**
II	17 (63.0)	10 (37.0)	**27 (27.0)**
III	6 (37.5)	10 (62.5)	**16 (16.0)**
IV	14 (36.8)	24 (63.2)	**38 (38.0)**
Total	**47 (47.0)**	**53 (53.0)**	**100 (100)**

Discussion

The present study shows that in almost fifty per cent of the patients with a squamous cell carcinoma of the oral cavity leukoplakia coexists. This finding and the fact that some oral leukoplakias undergo malignant transformation give support to the concept of leukoplakia being a potentially malignant or premalignant lesion.[14] The number of patients in the present with oral squamous cell carcinoma and adjacent leukoplakia (36 %) is in accordance with several reported studies (Table 1). The reported differences in oral squamous cell carcinoma associated with leukoplakia may be explained by variations in diagnostic criteria, case selection or referral bias (Table 1).

No gender predilection was noted in the present study with regard to the concomitant occurrence of leukoplakia and OSCC, which is in accordance with the study by Bouquot et al.[3] It has been shown in follow-up studies of oral leukoplakia, that women carry an increased risk of malignant transformation of oral leukoplakia .[15,16] Therefore, one would expect more women to have an OSCC to be associated with leukoplakia. The present study does not support this expectation. This discrepancy may be explained by the fact that most of the studies in which women apparently carry an increased risk of malignant transformation of leukoplakia were based on selected populations.

Although it has been reported in studies on collected leukoplakias, that location on the tongue or the floor of mouth may have an increased risk of malignant transformation in comparison to other oral subsites [17,18] ,the present study did not show a relation to a specific site of the carcinoma with respect to the presence or absence of concomitant leukoplakia.

It has been stated that mucosal carcinomas associated with leukoplakia appear to be smaller, are histologically more mature, and are more likely to be only superficially invasive, and, therefore, provide a better prognosis than similar carcinomas not associated with leukoplakia.[3] The variety of oral subsites, and TNM stages, and the number of cases involved in the present study does not

allow to statistically demonstrate a possible difference in prognosis between oral cancer patients with and without concomitant leukoplakia. In a study of 522 patients with a diagnosis of squamous cell carcinoma or carcinoma-in-situ of the tongue the subgroup of patients with concomitant leukoplakia, showed a five times greater incidence of the development of subsequent multiple oral carcinomas of the oral cavity and pharynx, than patients without leukoplakia, which likely results in a poorer prognosis.[19] In the present study no specific independent clinical or histopathological features between OSCC with or without leukoplakia were encountered.

Conclusion

Almost fifty per cent of oral squamous cell carcinomas may be preceded by or associated with leukoplakia. Early detection and active management of patients with oral leukoplakia may prevent the development of a number of oral squamous cell carcinomas.

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- Chapter 7 -

TOBACCO USAGE IN RELATION TO THE ANATOMICAL SITE OF ORAL LEUKOPLAKIA

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Abstract
Tobacco usage is the most important known aetiological factor in the development of oral leukoplakia.
Objective: To investigate the possible relation of tobacco usage to the anatomical site of the leukoplakia.
Patients and methods: Clinical data regarding tobacco usage and localisation of leukoplakia obtained from 166 patients with oral leukoplakia.
Results: Leukoplakias in the floor of mouth appeared to be statistically significantly more often present in smokers than in non-smokers, compared to all other oral sites ($p < 0.001$; OR = 8.47 and 18.13 for men and women, respectively). On the contrary, leukoplakias on the borders of the tongue were statistically significantly more common among non-smokers, than smokers, compared to all other oral sites ($p < 0.001$; OR = 0.22
and 0.12 for men and women, respectively).
Conclusion: The present study suggests that the influence of tobacco on the development of leukoplakia varies by anatomical site.

Introduction
Tobacco usage is the most important known aetiological factor in the development of oral leukoplakia. Patients who smoke have a sixfold increased risk of developing leukoplakia of the oral mucosa than non-smokers.[1] Leukoplakia in non-smokers is often referred to as 'idiopathic leukoplakia'. The site of the leukoplakia depends, among other things, on the type of the smoking habit, the quality, and the quantity of the tobacco.[2] The purpose of the present study is to evaluate possible differences between smokers and non-smokers with regard to the anatomical site of their leukoplakia.

Patients and Methods
Data were obtained from 166 patients with oral leukoplakia, who were referred to the Department of Oral and Maxillofacial Surgery at the Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands. Leukoplakia has been defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion.[3]
Since there were only five patients with leukoplakia of the lips, these patients were excluded. The remaining group of 161 patients consisted of 73 men and 88 women. The mean age was 57 years (range 23 – 91 years). Further details of this population have been described elsewhere.[4]
Data about the usage of tobacco were obtained from the patients records at the time of diagnosis of the leukoplakia. Fifteen patients were excluded from further evaluation, because insufficient available data about their smoking habits. In the remaining group of 146 patients, a distinction was made only between smokers (almost exclusively cigarettes) and non-smokers.
The localisation of the leukoplakias was specified according to the anatomical distribution recommended by the ICD-DA.[5] For analysis of a possible relation of tobacco usage and the localisation of leukoplakia four oral subsites and a category of 'multiple sites' were studied, separately for men and women. The relation was expressed as an Odds Ratio (OR) with 95%- confidence interval. Statistical significance was assessed using the Chi-square test, with p-values less than 0.05 considered significant.

Results
Table 1 shows the distribution of smokers and non-smokers according to gender for the study population of 146 patients, together with the mean ages. Remarkable is the difference in mean age between female smokers and non-smokers.
The distribution of smokers and non-smokers according to oral (sub)site of the leukoplakia is shown in Table 2. Leukoplakias of the cheek mucosa, including

the commissures, were found more often in men who smoke, than in men who did not. Among women, this difference was not noted. Leukoplakias in the floor of the mouth appeared to be statistically significantly more often present in smokers than in non-smokers, compared to all other oral subsites (both men and women, $p < 0.001$). Leukoplakias on the borders of the tongue were statistically significantly more common among non-smokers than smokers, compared to all other oral subsites (both men and women, $p < 0.001$).

Table 1: Mean ages (years) and number (n)of men and women with oral leukoplakia in smokers and non-smokers .

	Smoker Mean age (n)	Non-smoker Mean age (n)	Mean age (n)
Men	57.4 (44)	56.6 (24)	57.1 (68)
Women	48.8 (47)	65.6 (31)	55.7 (78)
Overall	**53.1 (91)**	**61.7 (55)**	**56.4 (146)**

Table 2: Distribution of oral (sub)site of the leukoplakia according to smokers (S) and non-smokers (NS), subdivided according to gender.

Localisation	Men		Women		Total
	S	NS	S	NS	
Cheek mucosa (including commissures)	11	1	6	5	**23**
Gingiva upper/lower, palate	6	6	4	3	**19**
Borders tongue	10	14	7	19	**50**
Floor of mouth	12	1	17	1	**31**
Multiple sites	5	2	13	3	**23**
Total	**44**	**24**	**47**	**31**	**146**

The odds ratios (ORs) for the oral subsites related to the use of tobacco according to gender are shown in Table 3; the total number of all other oral subsites were used as the reference group for each individual subsite. The highest ORs for men were seen in the floor of mouth and in the cheek mucosa, being 8.47 and 7.54 respectively. The highest OR for women was seen for the floor of mouth (OR = 18.13). The lowest OR for men and women was seen for leukoplakias on the borders of the tongue (0.22 and 0.12, respectively).

Table 3: Odds ratios (ORs) for the use of tobacco of oral leukoplakia of the various oral subsites related to all other localisations according to gender.

Oral subsite	Men		Women	
	OR	95%CI	OR	95%CI
Cheek mucosa (including commissures)	7.54	1.41 – 39.93	0.82	0.25 – 2.67
Gingiva upper/lower, palate	0.48	0.14 – 1.62	0.93	0.16 – 5.50
Borders tongue	0.22	0.08 – 0.62	0.12	0.04 – 0.34
Floor of mouth	8.47	1.41 – 50.97	18.13	3.58 – 91.95
Multiple sites	1.40	0.28 – 6.99	3.82	0.23 – 60.25

OR = Odds ratio; CI = confidence interval

Discussion

The results of the present study suggest that the influence of tobacco on the development of oral leukoplakia varies by anatomical subsite. This finding is in accordance with that of a study about the role of tobacco related to the anatomical subsite for the development of oral squamous cell carcinoma.[6] Our study shows that in smokers the floor of mouth is the site of predilection for oral leukoplakia, whereas the borders of the tongue are affected statistically significantly more often in non-smokers. The OR of 8.47 in men for a leukoplakia located in the floor of mouth means that leukoplakia in the floor of mouth is approximately 8.5 times more likely to occur in a smoker than in a non-smoker. The accompanying confidence interval (C.I.) (1.41 – 50.97) is with 1.41, on the minimum side, rather low. However, the OR of 18.13 in women for a leukoplakia located in the floor of mouth shows a rather high C.I. (minimum of 3.82), which means that leukoplakia in the floor of mouth in women is at least approximately 4 times more likely to occur in women who smoke than women who do not smoke. There is no explanation for the gender differences with respect to the differences in the site of predilection for leukoplakia in the cheek mucosa in men who smoke, and leukoplakia located in the floor of mouth in women who smoke. Highly speculative would be that men and women would exhibit a different way of placing the cigarrete between their lips; men keep their cigarette perhaps more to the side of their lips, while women might keep the cigarette more centered.

The apparently strong local effect of smoking on the development of leukoplakia in the floor of mouth in smokers may be explained by the fact that saliva in this oral subsite acts as a reservoir for carcinogens in tobacco products.[7] Furthermore, the degree of keratinisation and the permeability of the oral mucosa may play a role in the local effect of tobacco products.[8,9] Different tobacco habits may play a role in the distribution of leukoplakia in the various

oral subsites as well. In The Netherlands, smoking cigarettes is the most common form of tobacco usage.[10] In the present study 64 % of the men were smokers, and 60.3 % of the women were smokers, whereas the proportion of the adult population in The Netherlands, smoking tobacco is 36.7 % and 30.3 % for men and women, respectively.[11] Including the proportion of ex-smokers, these percentages for the adult population for men and women would be 56.0 % and 45.5 %, respectively[11]; still significantly less than the patients with oral leukoplakia in this study, which supports the causative relation between smoking and the development of oral leukoplakia.

Various reports have suggested a synergistic effect of tobacco and alcohol usage in oral carcinogenesis.[12,13] Alcohol usage alone probably does not play a major role in the aetiology of oral leukoplakia, but may have a similar synergistic effect on the development of leukoplakia as has been reported in oral squamous cell carcinoma.[14] The limited information about alcohol consumption in our group of patients did not allow statistical analysis in this respect.

Various reports showed an inreased risk of malignant transformation of leukoplakia in women without smoking habits.[15,16] This was also the case in the present material, reported elsewhere.[4] The association of an increased risk of malignant transformation of oral leukoplakia in women who do not smoke remains unclear.

Conclusion

Tobacco usage in men results significantly more often in leukoplakia of the cheek mucosa, including the commissures, than in men who do not smoke. This difference is not noted among women. Furthermore, leukoplakia of the floor of mouth almost exclusively occurs in smokers, either men or women. Interestingly, leukoplakia of the borders of the tongue is relatively more common in women who do not smoke. The various limitations of the present retrospective study do not allow further speculation about the significance of the abovementioned observations.

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- Chapter 8 –

SUMMARY AND RECOMMENDATIONS

Summary and recommendations:

This thesis encompasses a clinicopathological study on oral leukoplakia based on a recently, internationally revised definition. Oral leukoplakia is a premalignant, or synonymously, potentially malignant or precancerous lesion, presently being defined as 'A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some leukoplakias will transform into cancer'.

In **chapter 1** a general introduction and the aim and outline of the study have been presented.

Chapter 2 an overview of the literature is given. Special reference is given with regard to the definition and terminology, as well as the management of oral leukoplakia (Appendix I).
In patients with oral leukoplakia and who smoke, the term "tobacco-associated" leukoplakia may be used in the phase of the preliminary clinical diagnosis. If the lesion disappears after cessation of the smoking habits, such lesion should be called, in retrospect, a smoker's lesion. If the lesion does not regress after the cessation of the smoking habits, or if the patient does not stop the habit, there seems no reason to maintain the term "tobacco-associated" leukoplakia, giving preference to the single term leukoplakia, instead.
In appendix I a slightly modified flow diagram has been presented for the diagnosis and management of oral leukoplakia. In addition a *certainty* (C) factor has been applied, more or less analogous to what has been recommended for the TNM system in the Classification of Malignant Tumours. This resulted in the following subdivision:

- L_{C1} - Leukoplakia as a provisional clinical diagnosis (based on clinical judgement during one visit)
- L_{C2} - Leukoplakia as a definitive clinical diagnosis (based on observation of the results of the elimination of possible causative factors or in the absence of any possible causative factors)
- L_{C3} - Leukoplakia for which a biopsy has been taken (either classified as dysplastic or non-dysplastic leukoplakia)

In **chapter 3** the preliminary experiences with a new classification and staging system based on the revised definition of oral leukoplakia have been described. A group of 100 patients with a diagnosis of oral leukoplakia was subjected to this classification and staging system. The classification and staging seem to be especially suitable for uniform reporting. The significance of this system for the management and prognosis for patients with oral leukoplakia requires further

investigation. Furthermore, a suggestion for revision of this system has been put forward (Appendix II).

In **chapter 4** the experiences with, and the implications of the revised definition of oral leukoplakia, including a distinction between a provisional and a definitive diagnosis, in an epidemiological study have been described based on of a prevalence study of oral white lesions. The prevalence of a provisional and a definitive diagnosis of leukoplakia were respectively 0.6 and 0.2 per cent. It was concluded that the use of the revised definition, as well as the classification and staging system used mentioned before, both were very suitable for epidemiological studies.

In **chapter 5** malignant transformation has been investigated in a follow-up study of 166 patients with a diagnosis of leukoplakia of the oral cavity. Malignant transformation occurred in 20 (12%) of the 166 patients in a median follow-up period of 29 months. The estimated malignant transformation rate was calculated at 2.9 % per year. Features associated with an increased risk for malignant transformation were, in random order, (1) women without tobacco habits, (2) a non-homogeneous clinical aspect, and (3) dysplastic changes on histopathological examination. However, malignant transformation has been observed in homogeneous leukoplakias without distinct features of epithelial dysplasia. There were no specific sites with an increased risk for malignant transformation. It was concluded that the importance of certain said risk factors, such as oral subsite and clinical aspect, associated with an increased risk of malignant transformation should not be overestimated. 'Innocuous' leukoplakias may transform into cancer as well.
The latter observation may be due to a sampling error in the taking of the incisional biopsy procedure. Futhermore, incorrect histological assessment of the absence of epithelial dysplasia may have occurred, which calls for better quantification of this assessment and probably also for the application of other examination techniques, including (immunohistochemical) markers, e.g. suprabasal presence of mutant p53 gene[1], loss of heterozygosity at 3p and/or 9q,[2-5] the use of proliferation markers (particularly Ki-67 (Mib-1),[6] or epidermal growth factor receptor genes (erbB-1 and erbB-2).[7]
Interestingly, patients who had any form of intervention did not have statistically significantly lower chance for malignant transformation than patients who were kept under surveillance without intervention, at least as shown in our retrospective study. This finding is difficult to interprete, mainly because of the already mentioned retrospective nature of our study, particularly with regard to the lack of reliable information about the criteria that have been used for intervention versus a wait-and-see policy. Generally, it is actually unknown whether active treatment truly prevents the occurrence of cancer. Future prospective randomized studies should give an answer to this question. Until

effective therapies are developed to prevent malignant transformation of oral leukoplakia removal of oral leukoplakia still seems to be the most logical way to try to prevent future malignant transformation.[8]
The design of our study did not allow to make firm recommendations with regard to the intervals and length of follow-up both in treated and untreated patients with oral leukoplakia. In the literature no cost-benefits studies are available on this subject.

In **chapter 6** a study has been described of 100 consecutive patients, with a histologically proven squamous cell carcinoma of the oral cavity (OSCC) for the presence of concomitant leukoplakia. Thirty six per cent of the patients had leukoplakia adjacent to the OSCC, of whom 8 patients also had a leukoplakia at another oral site. Eleven per cent of the patients had no leukoplakia adjacent to the OSCC, but did have a leukoplakia at another oral site. Fifty-three per cent of the patients with an OSCC had no concomitant leukoplakia. There were no statistically significant differences between OSCC's with or without concomitant leukoplakia with respect to gender, a oral subsite, grade of differentiation on histological examination, nor stage grouping of the OSCC. It has been concluded that, almost 50 % of the OSCC's may be preceded by or associated with leukoplakia. This finding further suggests that early detection and active management of patients with oral leukoplakia may prevent the development of a significant number of oral squamous cell carcinomas, although the evidence for the effectiveness of intervention still has to be proven (Chapter 5).

In **Chapter 7** a group of 146 patients with a leukoplakia of the oral cavity has been investigated for the possible relation of smoking habits on the distribution of the localisation of the leukoplakia. Leukoplakias of the cheek mucosa and commissures were found more often in men who smoke, than in men who do not smoke. Leukoplakias in the floor of mouth appeared to be statistically significantly more often present in smokers than in non-smokers, compared to all other subsites, both for men and women ($p < 0.001$). Leukoplakias on the borders of the tongue were statistically significantly more common among non-smokers than smokers, compared to all other oral subsites (both men and women; $p < 0.001$). This study showed that in smokers the floor of mouth is the site of predilection for oral leukoplakia, whereas the borders of the tongue are affected statistically significantly more often in non-smokers. The results of this study suggest that the influence of tobacco on the development of oral leukoplakia varies by anatomical site.

The following main conclusions and recommendations can be drawn from the present study:

- Suggestions for a more precise use of the definition and terminology of oral leukoplakia and allied lesions with a white appearance have been made. These still require validation.

- Introduction of a classification and staging system for oral leukoplakia with the main purpose of uniform reporting.

- There is a need for a prospective study with regard to the effectiveness of intervention in patients with oral leukoplakia with regard to possible malignant transformation. This also applies to the effectiveness of the various treatment modalities, e.g. cold-knife excision, CO_2-laser evaporation, topical application or systemic administration of retinoids.

- Confirmation of the increased risk of malignant transformation of oral leukoplakia in women who do not smoke.

- Confirmation of the prognostic value of the presence of epithelial dysplasia as assessed by light microscopy. However, in view of the observed malignant transformation in patients with apparently non-dysplastic leukoplakia, there is a need for additional markers of possible malignant transformation.

- The presumed high risk sites for malignant transformation of oral leukoplakia, being the tongue and the floor of the mouth, have not been confirmed in the present study.

- In contrast with that what often has been suggested, oral cancer is often associated with or possibly preceeded by oral leukoplakia.

- Confirmation of the aetiologic role of tobacco use and the occurence of oral leukoplakia. The finding that leukoplakia of the floor of the mouth is almost exclusively seen in smokers, whereas this was the reverse in leukoplakia of the tongue, deserves further attention.

Samenvatting en aanbevelingen

Samenvatting en aanbevelingen:

Dit proefschrift betreft een klinisch-pathologische studie over orale leukoplakie gebaseerd op de recentelijk herziene internationale definitie. Orale leukoplakie is een premaligne, of potentieel maligne c.q. precancereuze laesie, gedefinieerd als 'een overwegend witte laesie van het mondslijmvlies die niet anders gekarakteriseerd kan worden als een andere definieerbare afwijking; sommige leukoplakieën ontaarden in kanker'.

In **hoofdstuk** 1 wordt in een algemene introductie het doel en de opzet van de studie uiteengezet.

In **hoofdstuk 2** wordt een overzicht van de literatuur gegeven. Hierbij is speciale aandacht besteed aan de definitie en terminologie, alsmede het management van orale leukoplakie (Appendix I).
Bij patiënten met orale leukoplakie die roken kan de term "tabak-geassocieerde" leukoplakie gebruikt worden in het stadium van een voorlopige klinische diagnose. Als de laesie verdwijnt na het staken van de rookgewoonte, dan moet deze laesie met terugwerkende kracht een 'rokers-laesie' genoemd worden. Als de laesie na het stoppen van het roken niet in regressie gaat, of wanneer de patiënt niet stopt met roken, dan is er geen reden de term "tabak-geassocieerde laesie" te handhaven. In plaats daarvan gaat de voorkeur uit naar de term 'leukoplakie'.
In Appendix I wordt een enigszins gemodificeerd stroomdiagram getoond met betrekking tot het stellen van de diagnose en het management van orale leukoplakie. Hieraan is een 'certainty' (C) factor toegevoegd, min of meer analoog aan het TNM systeem voor de klassificatie van maligne tumoren, resulterend in de volgende onderverdeling:

- L_{C1} - Leukoplakie als voorlopige klinische diagnose (gebaseerd op de klinische beoordeling van één bezoek)
- L_{C2} - Leukoplakie als een definitieve klinische diagnose (gebaseerd op de resultaten van eliminatie van mogelijke oorzakelijke factoren of bij afwezigheid van mogelijk oorzakelijke factoren)
- L_{C3} - Leukoplakie waarvan een biopsie genomen is (geklassificeerd als dysplastische of niet-dysplastische leukoplakie)

In **hoofdstuk 3** worden de eerste ervaringen beschreven met een nieuw klassificatie en stadiëringssyteem gebaseerd op de herziene definitie van orale leukoplakie. De patiëntengegevens van een groep van 100 patiënten met orale leukoplakie werd onderworpen aan dit klassificatie en stadiëringsysteem. De klassificatie en stadiëring blijkt vooral geschikt voor eensluidende verslaglegging. De betekenis van dit systeem voor het management en prognose

voor patiënten met orale leukoplakie vereist verder onderzoek. Bovendien wordt een voorstel gedaan voor een revisie van dit systeem (Appendix II).

In **hoofdstuk 4** worden in een epidemiologische studie, gebaseerd op een prevalentie studie naar witte lesies van het mondslijmvlies, de ervaringen en implicaties besproken van de herziene definitie van orale leukoplakie met inbegrip van een onderscheid tussen een voorlopige en een definitieve diagnose. De prevalentie van een voorlopige en een definitieve diagnose leukoplakie zijn respectievelijk 0,6 en 0,2 procent. Geconcludeerd wordt dat zowel de herziene definitie, als het gebruikte klassificatie - en stadiëringssysteem voor orale leukoplakie zeer geschikt zijn bij epidemiologische studies.

In **hoofdstuk 5** wordt maligne transformatie onderzocht aan de hand van een follow-up studie met 166 patiënten met diagnose leukoplakie van het mondslijmvlies. Maligne transformatie trad op bij 20 (12 %) van de 166 patiënten in een mediane follow-up periode van 29 maanden. De geschatte maligne transformatie ratio was 2,9 % per jaar. Kenmerken geassocieerd met een verhoogd risico op maligne transformatie waren, in willekeurige volgorde, (1) vrouwen die niet roken, (2) een niet-homogeen klinisch aspect, en (3) dysplastische veranderingen bij histopathologisch onderzoek. Maligne transformatie vond echter ook plaats bij homogene leukoplakieën zonder evidente aanwijzingen voor epitheel dysplasie. Er waren geen specifieke localisaties met een verhoogd risico op maligne transformatie. Geconcludeerd werd dat het belang van zogenaamde risico factoren, zoals de localisatie en het klinische aspect, geassocieerd met een verhoogde kans op maligne transformatie niet overschat moet worden, daar ogenschijnlijk 'onschuldige' leukoplakieën eveneens kunnen overgaan in kanker.
De laatstgenoemde opmerking is mogelijk toe te schrijven aan een niet representatief gekozen plaats voor de incisiebiopsie. Bovendien zou bij de histologische beoordeling de afwezigheid van epitheel dysplasie onjuist kunnen zijn vastgesteld. Een betere kwantificering van deze bepaling is vereist en vraagt derhalve om het gebruik van eventuele andere onderzoekstechnieken, inclusief het gebruik van (immunohistochemische) markers, zoals bijvoorbeeld het aantonen van de aanwezigheid van het mutant p53 gen suprabasillair[1], verlies van heterozygositeit op 3p en/of 9q[2-5], het gebruik van proliferatiemarkers (met name Ki-67 (Mib-1)[6], of epidermale groeifactor receptor genen (erbB-1 en erbB-2).[7]
Interessant was het gegeven dat bij patiënten met enige vorm van interventie de kans op maligne transformatie *niet* statistisch significant lager was, dan bij patiënten die regelmatig gecontroleerd werden zonder enige vorm van interventie, tenminste zoals aangetoond in onze retrospectieve studie. Deze bevinding is moeilijk te interpreteren, voornamelijk vanwege het reeds genoemde retrospectieve karakter van onze studie en het gebrek aan

betrouwbare informatie over de gebruikte criteria voor interventie tegenover een expectatief beleid. Het is eigenlijk niet bekend of actieve behandeling daadwerkelijk het ontstaan van kanker voorkomt. Prospectieve gerandomiseerde studies zouden in de toekomst antwoord op deze vraag moeten geven. Totdat effectieve therapieën zijn ontwikkeld ter voorkoming van maligne transformatie van orale leukoplakie, lijkt verwijdering van de leukoplakie nog steeds de meest logische manier om een mogelijk toekomstige maligne transformatie te voorkomen.[8]
De opzet van onze studie stond niet toe harde aanbevelingen te doen met betrekking tot het interval en de lengte van de follow-up bij behandelde en onbehandelde patiënten met oral leukoplakie.
Er zijn in de literatuur geen kosten-baten studies beschikbaar over dit onderwerp.

Hoofdstuk 6 beschrijft een studie van 100 patiënten met een histologisch bewezen plaveiselcarcinoom (PCC) van de mondholte naar het gelijktijdig voorkomen van leukoplakie. Zessendertig procent van de patiënten hadden leukoplakie aangrenzend aan het PCC, waarvan acht patiënten tevens een leukoplakie op een andere localisatie in de mondholte hadden. Elf procent van de patiënten hadden geen leukoplakie grenzend aan het PCC, maar hadden wel een leukoplakie op een andere localisatie in de mondholte. Drieënvijftig procent van de patiënten met een PCC hadden geen gelijktijdig voorkomende leukoplakie. Er waren geen statistisch significantie verschillen tussen PCC-en met of zonder gelijktijdige leukoplakie met betrekking tot geslacht, localisatie in de mondholte, mate van differentiatie bij histologisch onderzoek, noch bij stadiëring van het PCC. Geconcludeerd werd dat ongeveer 50 % van de PCC-en voorafgegaan kunnen worden of geassocieerd zijn met leukoplakie. Deze bevinding suggereert tevens dat vroege ontdekking en actieve behandeling van patiënten met orale leukoplakie het ontstaan van een aanzienlijk aantal plaveiselcelcarcinomen zou kunnen voorkomen, hoewel de effectiviteit van interventie nog bewezen moet worden (hoofdstuk 5).

Hoofdstuk 7 beschrijft een onderzoek naar de mogelijke relatie van rookgewoonten en de verdeling naar localisatie van de leukoplakie bij een groep van 146 patiënten. Leukoplakieën van het wangslijmvlies en commissuren werden vaker bij mannen die rookten gevonden, dan bij mannen die niet rookten. Zowel bij mannen als bij vrouwen bleken leukoplakieën van het mondbodemslijmvlies statistisch significant vaker aanwezig bij rokers, dan bij niet-rokers, vergeleken met de overige localisaties in de mondholte ($p<0,001$). Leukoplakieën op de tongranden waren statistisch significant vaker aanwezig bij niet-rokers dan bij rokers in vergelijking met alle overige localisaties (zowel bij mannen als bij vrouwen; $p<0,001$). Deze studie toonde aan dat het mondbodemslijmvlies de voorkeurslocalisatie is voor het ontstaan van orale

leukoplakie bij rokers, in tegenstelling tot leukoplakieën van de tongranden, die statistisch significant vaker voorkwamen bij niet-rokers. De resultaten van deze studie suggeren dat de invloed van roken op het ontstaan van orale leukoplakie varieert per anatomische localisatie.

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De voornaamste conclusies en aanbevelingen van de huidige studie zijn:

- Er zijn duidelijker suggesties gemaakt voor het gebruik van de definitie en terminologie van orale leukoplakie en aanverwante lesies met een witte verschijningsvorm. Deze vereisen echter nog validering.

- De introductie van een klassificatie en stadierings systeem voor orale leukoplakie met als hoofdzaak eenduidige verslaglegging.

- Er is behoefte aan een prospectieve studie naar het effect van interventie bij patienten met orale leukoplakie met betrekking tot maligne transformatie. Dit geldt ook voor het effect van de verschillende behandelingsmodaliteiten, bijvoorbeeld excisie met het mes, CO_2-laser verdamping, locale applicatie of systemische toediening van retinoiden.

- Bevestiging van het verhoogde risico op maligne transformatie van orale leukoplakie bij vrouwen die niet roken.

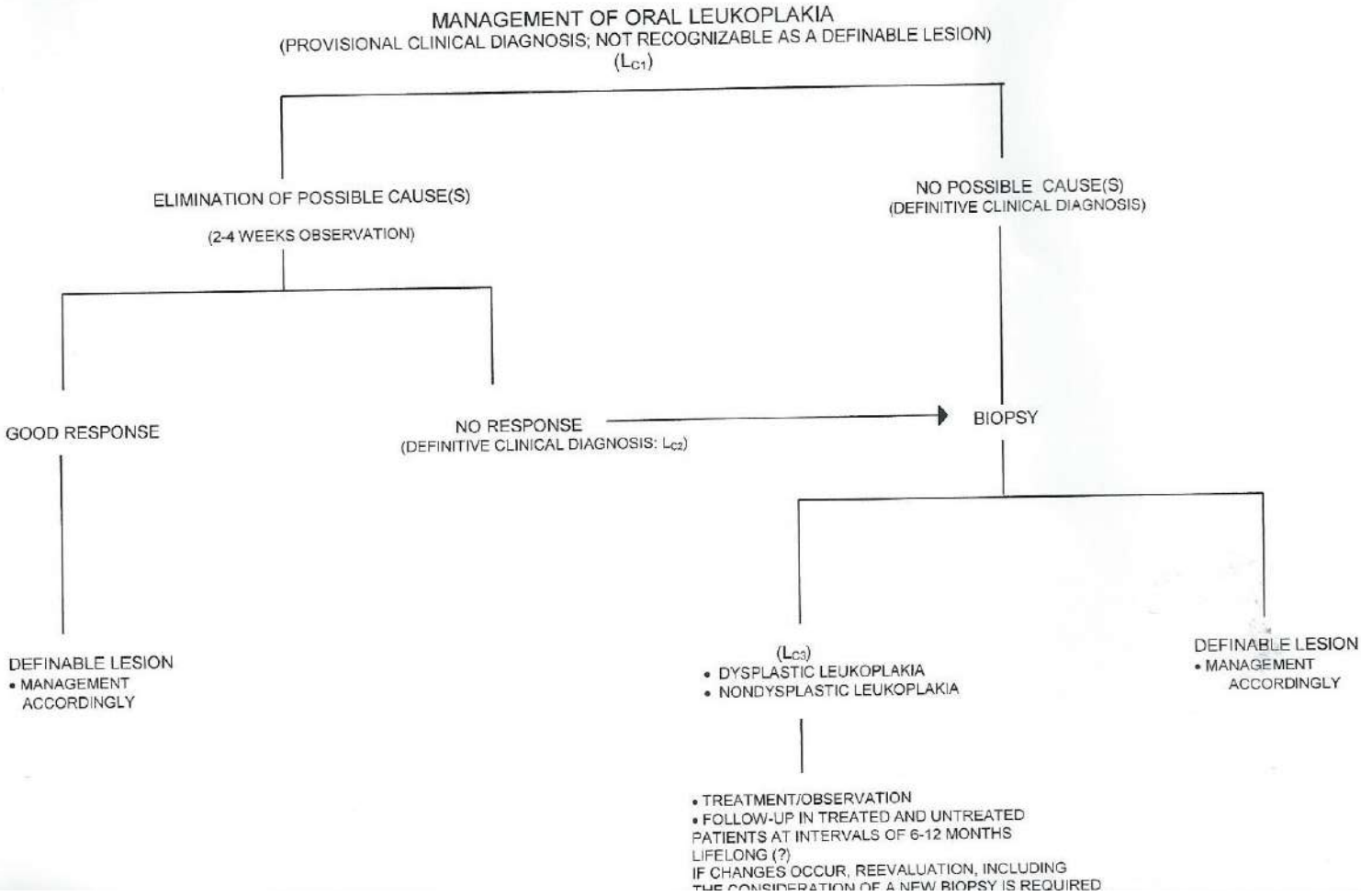
- Bevestiging van de prognostische waarde van de aanwezigheid van epitheeldysplasie vastgesteld door lichtmicroscopie; er is echter behoefte aan additionele markers voor mogelijke maligne transformatie vanwege de vastgestelde maligne transformatie bij patienten met een ogenschijnlijk niet-dysplastische leukoplakie.

- De veronderstelde 'high-risk' localisaties voor maligne transformatie van orale leukoplakie, te weten de tong en mondbodem, zijn in de huidige studie niet bevestigd.

- In tegenstelling tot wat vaak gesuggereerd wordt, is mondkanker vaak geassocieerd met orale leukoplakie of wordt hierdoor mogelijk voorafgegaan.

- Bevestiging van de aetiologische rol van tabaksgebruik en het voorkomen van orale leukoplakie; de bevinding dat leukoplakie van de mondbodem praktisch uitsluitend gezien wordt bij rokers, terwijl het omgekeerde het geval was bij leukoplakie van de tong, vereist nadere aandacht.

Appendix I: Diagnosis and management of oral leukoplakia



Appendix II

Revised classification and staging system for oral leukoplakia (OLEP)[1]

Classification system:

L (size of the leukoplakia)

L_1 - size of single or multiple leukoplakias together $\leq$ 2 cm

L_2 - size of single or multiple leukoplakias together 2-4 cm

L_3 - size of single or multiple leukoplakias together $\geq$ 4 cm

L_x - size not specified

P (pathology)

P_0 - no epithelial dysplasia (includes "no or perhaps mild epithelial dysplasia")

P_1 - distinct epithelial dysplasia (includes "mild to moderate" and "moderate to possibly severe" epithelial dysplasia)

P_x - absence or presence of epithelial dysplasia not specified in the pathology report

OLEP staging system:

Stage I - L_1P_0

Stage II - L_2P_0

Stage III - L_3P_0 or $L_1L_2P_1$

Stage IV - L_3P_1

General rules of the OLEP staging system:

1. If there is doubt concerning the correct L or P category to which a particular case should be allotted, than the lower (i.e. less advanced) category should be chosen. This will also be reflected in the stage grouping.
2. In case of multiple biopsies of single leukoplakia or biopsies taken from multiple leukoplakias the highest pathological score of the various biopsies should be used.
3. For reporting purposes the oral subsite according to the ICD-DA should be mentioned (World Health Organisation, International Classification of Diseases Tenth Revision. Application to Dentistry and Stomatology, ICD-DA, Geneva 1992).

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Curriculum vitae

Kees-Pieter Schepman werd geboren op 12 december 1964 te Zwartsluis. In 1986 behaalde hij het eindexamen Atheneum aan de Thorbecke scholengemeenschap te Zwolle, waarna hij de opleiding tot officier volgde bij de Koninklijke Landmacht.
In 1986 werd begonnen met de studie tandheelkunde aan het Academisch Centrum Tandheelkunde Amsterdam (ACTA). Het tandartsexamen werd behaald in 1993. Aansluitend begon hij als A.I.O. (Assistent-In-Opleiding) met het promotieonderzoek op de afdeling Mondziekten en Kaakchirurgie en Orale Pathologie, Vrije Universiteit/ ACTA te Amsterdam (Hoofd: prof.dr. I. van der Waal). Gelijktijdig werd een aanvang gemaakt met de studie geneeskunde aan de Vrije Universiteit te Amsterdam. In 1997 behaalde hij het doctoraalexamen van de studie geneeskunde. Sinds 1 september 1997 is hij in opleiding tot specialist in de Mondziekten en Kaakchirurgie (opleider: prof.dr. I. van der Waal).