The possible premalignant character of oral lichen planus and oral lichenoid lesions

a clinicopathological study

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Meij van der, Erik Harald
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VRIJE UNIVERSITEIT

The possible premalignant character of oral lichen planus and oral lichenoid lesions

A clinicopathological study

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door

Erik Harald van der Meij

geboren te Ede

promotor: prof.dr. I. van der Waal

Al het zwoegen van de mens is voor zijn mond

Prediker 6:7a

Voor mijn patiënten

CONTENTS

INTRODUCTION AND AIM OF THE STUDY

1. Introduction

Possible malignant transformation of oral lichen planus (OLP) is the subject of an ongoing and controversial discussion in the literature. A case of carcinoma arising in lichen planus of the oral mucous membrane was first described by Hallopeau in 1910 (1). Ever since, several clinicopathological follow-up studies and case reports have been published on this subject. Additionally, the past decade, a number of investigations have focused on the immunohistochemical and molecular biological side of this discussion.

1.1. Clinicopathological studies

The range of malignant transformation of OLP per year, based on mainly retrospective follow-up studies, varies between 0.04 and 1.74% (Table 1) (2-21). Some authors have, therefore, accepted that OLP is regarded to be premalignant or, synonymously, potentially malignant or precancerous, but the topic is still subject to some controversy (22-28). A precancerous lesion is defined as 'a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart', whereas a precancerous condition is defined as 'a generalized state associated with a significant increased risk of cancer' (29). Since OLP is regarded as a localized manifestation of a generalized disorder, OLP appears to be, if premalignant, a premalignant condition, rather than a premalignant lesion.

The major problem in the discussion on the possible premalignant character of OLP are the inclusion criteria that are used in the aforementioned follow-up studies (30). Since there are no universally accepted diagnostic criteria for OLP, the diagnostic approaches of the studies vary. In some, the diagnosis of OLP was based solely on clinical features (4,6), while others have used microscopical criteria (12), and yet others have included both clinical and histological criteria (3,5,7,11). It is well recognized that both clinical and histopathological criteria of OLP, such as proposed by the World Health Organization (WHO) in 1978 (31), leave room for subjectivity in the interpretation. Especially the plaque-type and also the erosive type of OLP may sometimes be difficult to distinguish clinically from the various manifestations of homogeneous and non-homogeneous leukoplakia.

It has long been known that the histopathological features of OLP may be accompanied by characteristics of epithelial dysplasia (32-36).

Table 1.
Studies on the possible malignant transformation of oral lichen planus (1970-2002)

Authors	Year	Country	# of OLP patients	# of cancer patients	MTR (%)	mean follow-up (years)	MTR per year (%)
Shklar[2]	1972	USA	600	3	0.5	unknown	***unknown***
Fulling[3]	1973	Denmark	225	1	0.4	3.6	***0.12***
Kövesi *et al.*[4]	1973	Hungary	274	1	0.4	unknown	***unknown***
Silverman *et al.*[5]	1985	USA	570	7	1.2	5.6	***0.22***
Murti *et al.*[6]	1986	India	702	3	0.4	5.1	***0.08***
Holmstrup *et al.*[7]	1988	Denmark	611	9	1.5	7.5	***0.20***
Salem[8]	1989	Saudi Arabia	72	4	5.6	3.2	***1.74***
Silverman *et al.*[9]	1991	USA	214	5	2.3	7.5	***0.31***
Sigurgeirsson *et al.*[10]	1991	Sweden	2071	8	0.4	9.9	***0.04***
Voûte *et al.*[11]	1992	The Netherlands	113	3	2.7	7.8	***0.34***
Barnard *et al.*[12]	1993	UK	241	8	3.3	unknown	***unknown***
Moncarz *et al.*[13]	1993	Israel	280	6	2.1	unknown	***unknown***
Gorsky *et al.*[14]	1996	Israel	157	2	1.3	1.5	***0.85***
Markopoulos *et al.*[15]	1997	Greece	326	4	1.3	4.8	***0.26***
Silverman *et al.*[16]	1997	USA	95	3	3.2	6.1	***0.52***
Lo Muzio *et al.*[17]	1998	Italy	263	13	4.9	5.7	***0.86***
Rajentheran *et al.*[18]	1999	UK	832	7	0.8	11.0	***0.07***
Mignogna *et al.*[19]	2001	Italy	502	18	3.6	unknown	***unknown***
Chainani-Wu *et al.*[20]	2001	USA	229	4	1.7	unknown	***unknown***
Eisen[21]	2001	USA	723	6	0.8	4.5	***0.18***

OLP = oral lichen planus
MTR = malignant transformation rate

Krutchkoff and Eisenberg proposed the term 'lichenoid dysplasia' (LD) for this form of slight epithelial dysplasia (23,37-40). Several authors have underlined the importance of excluding patients with histologic features qualifying for the diagnosis of epithelial dysplasia from studies of possible malignant development of OLP (7,23,30). The lack of objective criteria of epithelial dysplasia adds to the confusion (41-43). Further, features of epithelial dysplasia are not exclusive to premalignant lesions. Dysplastic features may be seen in a variety of obviously benign lesions. Therefore, even the finding of histologic features of mild epithelial dysplasia in OLP lesions does not necessarily suggest a premalignant nature of these lesions.

As to the type of OLP most likely to undergo malignant change, several authors have reported atrophic/ulcerative/erosive OLP lesions as the lesions with the greatest preponderance for malignant development (4-7,9,12,44). These forms possibly also account for the largest number of erroneously made clinical or histopathological diagnoses.

Another important aspect is the occurrence of erythroplakic lesions in OLP patients (33). These lesions are sharply demarcated red lesions, and histological examination usually reveals epithelial dysplasia. In some instances they may even harbor a squamous cell carcinoma. These erythroplakic lesions appear to develop in about 1% of the OLP patients according to a study by Holmstrup and Pindborg (33).

Recently, Migogna et al. concluded on their data of four cases of oral squamous cell carcinomas which occurred in OLP patients, that OLP-related squamous cell carcinoma may have a worse prognosis because of increased metastatic potential (45). All four tumours were initially stage I tumors with a mean thickness of 1.75 mm. Recent studies indicate a tumour thickness over 4 mm as predictive of nodal metastasis, but all four patients developed lymphnodal metastasis within six months of follow-up (46,47).

1.2. Immunohistochemical and molecular biological studies

A genetic model for head and neck squamous cell carcinoma was proposed by Califano et al., demonstrating the accumulation of sequential genetic events during progression from benign epithelial hyperplasia to dysplasia to invasive carcinoma (48). Remembering the carcinogenic mechanism of field cancerization and the multistep process in oral squamous cell carcinoma, quantitation of the degree of chromosomal

change could reflect the degree of risk of cancer development in a target tissue. The genetic instability causing cancer development includes point mutations, amplification, deletion, abnormalities of chromosomal structure and arrangement, and chromosomal aneuploidy. Evaluation of the degree of genetic instability has to be useful in determining the possible premalignant potential of OLP, and if so, in identifying at-risk lesions. Several studies have therefore focused on this subject and have addressed potential genetic and molecular markers.

1.2.1 Allelotyping: loss of heterozygosity

Zhang and coworkers used microsatellite analysis to evaluate OLP for loss of heterozygosity (LOH) at loci on three chromosomal arms (3p, 9p, and 17p) (49). Loss on these arms is a common event in oral epithelial dysplasia and has been associated with risk of progression of oral leukoplakia to cancer (48,50-54). The data showed that, although dysplastic epithelium demonstrated a high frequency of LOH (40% for mild dysplasia), a significantly lower frequency of LOH was noted in OLP (6%), which was even lower than that in hyperplasia (14%). Those results did not support OLP as a lesion at risk for malignant transformation. As a second step of their research, they determined LOH frequencies in 61 dysplastic lichenoid lesions using the same microsatellite markers and compared these results with data obtained from the first study and from normal mucosal specimens (55). Dysplastic lichenoid lesions showed a high frequency of loss, but values did not differ significantly from those observed in dysplasia of similar degree without lichenoid appearance. None of the normal mucosa demonstrated LOH. From these data the authors concluded that epithelial dysplasia is a sign of malignant risk, independent of lichenoid changes, and that caution should be used when discounting dysplasia as being merely a reactive condition in lichenoid lesions.

1.2.2. p53 protein

Tumour suppressor genes, particularly p53, participate in the control of the transition from G1 to the S and G2 phases of cell cycle. The current concept is that normal p53, through its product -nuclear phosphoprotein-, is a key cell cycle check point, arresting cells in G1 to allow repair of

genetic damage. Alternatively, genetic lesions that inactivate p53 liberate cells from the constraint imposed by this gene, resulting in dysregulation of cell proliferation and maturation. When additional genetic changes are present in cells, according to the multistep process of carcinogenesis, neoplasm may arise. In head and neck squamous cell carcinoma p53 mutation and deletions have been reported to be common implicated genetic events (56-59). Several studies have, therefore, been conducted to investigate the expression of p53 in specimens from patients with OLP.

Immunohistochemical detection of p53 protein in OLP has varied between published studies. One group found no p53 protein expression by keratinocytes in OLP (60), while other groups detected positive staining in 19 – 64% of cases (61-67). From this positive staining it was inferred that the p53 staining in OLP may be due to mutant protein, further suggesting increased risk of malignant transformation of OLP. However, Dekker et al., finding abundant p53 protein-positive keratinocytes in all their investigated OLP cases, concluded that p53 staining in OLP is due to overexpression of wild-type protein and not mutant protein (68). Up-regulation of wild-type p53 protein, which would result in the arrest of the cell cycle, would be advantageous in OLP, because it would allow keratinocytes the opportunity to repair damaged DNA that may have been mediated by the lymhophagocytic infiltrate. It would plausibly follow that basal keratinocytes that were more severely damaged would undergo apoptosis, resulting in the typical interface features of OLP. These conclusions have been supported by investigators who were not able to detect mutations on the p53 gene itself (56,69).

1.2.3. Cytogenetic analysis

A recent study by Kim et al. assessed interphase cytogenetics to compare the degree of genetic instability between fifteen cases of steroid-responsive OLP and two cases of lichenoid dysplasia that progressed to squamous cell carcinoma (70). Chromosome in situ hybridisation was performed for chromosomes 9 and 17. The fraction of polysomic and monosomic cells for chromosome 9 increased significantly in mucosal epithelium compared to those of lymphocytes in OLP, and even more in cases of LD. It was suggested that the tumour suppressor gene in chromosome 9 might play a role in progression from OLP or LD to squamous cell carcinoma.

1.2.4. Miscellaneous studies

A number of studies have investigated potential genetic and molecular markers, including α9 integrin (71), matrix metalloproteinases (MMP-1 and -2) and their tissue inhibitors (TIMP-1, -2, -3) (72), laminin-5 (73), c-erbB-2 (74-76), thrombomodulin (77), tumour necrosis factor (TNF) and the 55-kDa TNF receptor (78), 5T4 oncofoetal antigen (79), telomerase (80), and Fhit tumour suppressor protein (81) with regard to the possible premalignant character of OLP. However, because of contradictory results and limited number of patients studied no final conclusions can be drawn from these data.

2. Aim of the present study

As discussed above, the possible premalignant character of OLP and oral lichenoid lesions (OLL) still remains a matter of debate. In this thesis the possible premalignant nature of OLP and OLL has been investigated. In *chapter 1* a critical review of literature relative to alleged malignant transformations of OLP has been performed with emphasis on the inclusion criteria used in these studies and the clinical and histopathological documentation of the malignant transformed cases. In *chapter 2 and 3* the intraobserver and interobserver variability in the histopathological and clinical assessment have been evaluated, applying the WHO definition of OLP from 1978. The degree of correlation between the clinical and histopathological assessment has been studied in *chapter 4*. Additionally, a proposal for a set of revised diagnostic criteria of OLP and OLL, based on the WHO definition of OLP, has been made. *Chapter 5* describes the possible premalignant character of OLP and OLL of a prospectively followed cohort of patients with detailed documentary data applying the proposed revised criteria of OLP and OLL. In *chapter 6* costs and effectiveness of screening for oral cancer in OLP and OLL patients have been calculated with a decision model. Besides, comparison of the cost-effectiveness of different screening scenarios, as well as a sensitivity analysis of several variables used in this model have been performed.

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CHAPTER 1

A REVIEW OF THE RECENT LITERATURE REGARDING MALIGNANT TRANSFORMATION OF ORAL LICHEN PLANUS

E.H. van der Meij[1]
K.P. Schepman[2]
L.E. Smeele[1]
J.E. van der Wal[1]
P.D. Bezemer[3]
I. van der Waal[1]

1 Department of Oral and Maxillofacial Surgery/Oral Pathology, Academic Centre for Dentistry Amsterdam (ACTA)/Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

2 Department of Oral and Maxillofacial Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

3 Department of Epidemiology and Biostatistics, Faculty of Medicine, Vrije Universiteit, Amsterdam, The Netherlands

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Abstract

On the basis of a literature review of the period 1950-1976, Krutchkoff et al. questioned the possible premalignant nature of OLP. Their criticism was largely based on insufficiencies of data in support of the initial diagnoses of the condition. In this treatise, a review of the literature from the period 1977-1999 has been described; the criteria used were those of Krutchkoff et al. Thirty-three of 98 (34%) reported cases were accepted as having sufficiently documented evidence of malignant transformation of OLP. Although this percentage is somewhat higher than the percentage reported by Krutchkoff et al., there apparently remains a need for uniformly accepted criteria to establish a firm diagnosis of OLP. Only when such criteria are available will it be possible to conduct long-term prospective studies on the suggested possible premalignant nature of OLP.

Introduction

It has been suggested that OLP is a rather common disease in the general population, the prevalence being between 1% and 2% in people over the age of 15 years (1). Although a number of authors have expressed the view that OLP is of a premalignant nature, the malignant transformation rate varying from 0.4 to 5.6% (2-32), Krutchkoff and others have criticized this opinion (33-35). These latter investigators reviewed the literature from the period 1950-1976 and accepted only 15 of 223 published cases as being sufficiently documented. Their criticism was largely based on 1) the insufficiency of the clinical and histopathological data to support the initial diagnosis of OLP, 2) the occurrence of some of the oral cancers in an anatomic site remote from the OLP, and 3) inadequate historical data regarding prior exposure to carcinogens (33). Since Krutchkoff's initial report, a continuing number of follow-up studies and case reports have been published on this subject. The present chapter will review these published accounts, applying the same criteria as those used by Krutchkoff et al..

Methods of evaluation

A MEDLINE search was performed of cases of OLP undergoing malignant transformation that were published in the English literature during the period January 1977 through January 1999. The same criteria that had been established by Krutchkoff et al. (33) for acceptance of a reported case as a bona fide example of malignant transformation in OLP were used (Table 1.1).

Table 1.1.
Criteria for acceptance of reported cases of OLP undergoing malignant transformation (Krutchkoff et al.) (33)

Original diagnosis
Clinical diagnosis must have been properly verified with histopathologic evidence demonstrating at least the last two of the following four features:

1. Hyper- or parakeratosis
2. Saw-toothed rete pegs
3. Superficial infiltrate of lymphocytes
4. Basal cell liquefaction

History and follow-up

1. Clinical and historical features of alleged transformation must have been adequately described (information such as age, sex, precise location and clinical description of the lesion are necessary).
2. Reported transformation should have had proper follow-up (minimum of two years) with all changes in clinical features properly recorded.

Tobacco exposure
Tobacco habits should have been properly documented to help distinguish between true malignant transformations and conventional carcinomas occurring in mouths of patients who happen to have lichen planus.

Table 1.2.
Summary of the literature relative to alleged malignant transformation of oral lichen planus (1977 – 1999)

Author(s) / Year	Number of Reported Transformations	Original Diagnosis		History and Follow-up		Tobacco Exposure	Case(s) Accepted
		Biopsy Performed	Histopathological Picture Demonstrating Feature 1, 2, 3 or 4 (see criteria)	Description of Clinical and Historical Features	Period of Follow-up		
HOLMSTRUP & PINDBORG / 1979 [2]	3	Yes	One case: 1 and 3 Two cases: 3	Well-described; illustrated with 2 clinical photographs	One case: 6 years Two cases: no follow-up	One case: non-smoker Two cases: light smoker	No
TYLDESLEY / 1982 [3]	1	Yes	3 and 4	Well-described; illustrated with 2 clinical photographs	7 years	Non-smoker	Yes
MARDER & DEESEN / 1982 [4]	1	Yes	1, 3 and 4	Well-described; illustrated with 6 clinical photographs	7 years	Heavy smoker	No
POGREL &WELDON / 1983 [5]	1	Yes	1, 3 and 4	Well-described; illustrated with 4 clinical photographs	2.5 years	Non-smoker	Yes
LIND et al. / 1985 [6]	1	Yes	1, 3 and 4	Poorly described	9 years	Unknown	No
KAPLAN & BARNES / 1985 [7]	1	Yes	1, 2, 3 and 4	Well-described	7 months	Non-smoker	No
SILVERMAN et al. / 1985 [8]	7	Yes	Unknown	Well-described	All patients were followed more than 2 years	Two cases: smokers Five cases: non-smokers	No
MURTI et al. / 1986 [9]	3	Yes	One case: 3 Two cases: unknown	Well-described; illustrated with 9 clinical photographs	All patients were followed more than 2 years	One case: smoker One case: chewer One case: mixed habit	No
FOWLER et al. / 1987 [10]	1	Yes	3 and 4	Well-described; illustrated with 2 clinical photographs	10 years	Non-smoker	Yes
HOLMSTRUP et al. / 1988 [11]	9	Yes	1, 3 and 4	Well-described; illustrated with 6 clinical photographs	All patients were followed more than 2 years	Four cases: light smokers Five cases: non-smokers	Yes
SALEM et al. / 1989 [12]	4	Yes	Not described	Not described	Unknown	Unknown	No
KATZ et al. / 1990 [13]	1	Yes	2, 3 and 4	Well-described; illustrated with 2 clinical photographs	10 years	Non-smoker	Yes
MASSA et al. / 1990 [14]	1	Yes	Not described	Well-described	No follow-up	Heavy smoker	No
SILVERMAN et al. / 1991 [15]	5	Yes	Not described	Poorly described	Range = 1 to 22 years	Unknown	No

Table 1.2. *continued*

Author(s) / Year	Number of Reported Transformations	Original Diagnosis		History and Follow-up		Tobacco Exposure	Case(s) Accepted
		Biopsy Performed	Histopathological Picture Demonstrating Feature 1, 2, 3 or 4 (see criteria)	Description of Clinical and Historical Features	Period of Follow-up		
SIGURGEIRSSON & LINDELÖF et al. / 1991 [16]	8	Yes	Not described	Not described	Unknown	Unknown	No
VOÛTE et al. / 1992 [17]	5	Three cases: yes Two cases: no	Not described	Poorly described	Three cases: > 2 years Two cases: no follow-up	Three cases: non-smokers One case: heavy smoker	No
BARNARD et al. / 1993 [18]	9	Yes	1, 3 and 4	Well-described	Three cases: < 2 years Six cases: > 2 years	Four cases: smokers Five cases: non-smokers	Four cases: yes Five cases: no
MONCARZ et al. / 1993 [19]	6	Yes	Not described	Not described	Five cases: no follow-up One case: > 2 years	Unknown	No
DUFFEY et al. / 1996 [20]	5	Yes	Not described	Well-described	One case: < 2 years Four cases: > 2 years	Two cases: smokers Three cases: non-smokers	No
GORSKY et al. / 1996 [21]	2	Yes	Not described	Poorly described	All patients were followed more than 2 years	Unknown	No
CARROZZO et al. / 1997 [22]	1	Yes	1, 3 and 4	Well-described; illustrated with 2 clinical photographs	2 years	Non-smoker	Yes
PORTER et al. / 1997 [23]	1	Yes	Not described	Well-described; illustrated with 1 clinical photograph	No follow-up	Non-smoker	No
MARKOPOULOS et al. / 1997 [24]	4	Yes	1, 3 and 4	Well-described; illustrated with 8 clinical photographs	All patients were followed more than 2 years	Non-smokers	Yes
SILVERMAN & BAHL / 1997 [25]	3	Unknown	Unknown	Well-described; illustrated with 2 clinical photographs	Range: 2 – 17.3 years	Non-smokers	No
LO MUZIO et al. / 1998 [26]	14	Yes	1, 3 and 4	Well-described; illustrated with 3 clinical photographs	All patients were followed more than 2 years	Four cases: smokers Ten cases: non-smokers	Ten cases: yes Four cases: no
CAMISA et al. / 1998 [27]	1	Yes	1, 3 and 4	Well-described; illustrated with 3 clinical photographs	7 years	Non-smoker	Yes

Results

A summary of all reported cases of OLP undergoing malignant transformation published during the period 1977-1999 is shown in table 1.2. Of 98 reported malignant transformations found in this survey, only 33 (34%) fulfilled all criteria and were thus accepted as sufficiently documented. Of the 65 rejected cases (66%), 20 were inadequately documented with regard to the histopathological criteria, one did not have proper documentation of the clinical and historical features of the OLP lesions, and 33 were neither histologically nor clinically documented. Four cases were rejected because of a follow-up less than two years and seven because of tobacco use.

Discussion

On the basis of their literature review in 1978, Krutchkoff et al concluded that there is little evidence that OLP is premalignant. They stated, however, that one should be aware of a possible transitional relationship between OLP and oral cancer but that further study of a larger number of adequately documented cases would be necessary before the exact nature of any interrelationship between these disease states could be determined (33). The present literature review reveals that most of the reported cases of malignant transformations that have been published since Krutchkoff's paper appeared are still insufficiently documented, mainly with regard to clinical and histopathological documentation.

Although the criteria for acceptance of a reported case that were used by Krutchkoff et al. have apparently not been validated, we choose to apply the same criteria; if we had done otherwise, comparison of the two reviews could not have been possible. Krutchkoff's final criterion is that tobacco habits should have been properly documented to help distinguish between true malignant transformations and conventional carcinomas occurring in mouths of patients who happen to have lichen planus. We are aware of the theoretic possibility that it would not be possible to make this distinction if all cases of transformation were to reveal a history of tobacco and if there were a true premalignant potential of registered OLP lesions at the same time. In the present review, seven (7%) such cases of tobacco exposure were rejected.

If the prevalence of OLP is set at 1% to 2% in the population over the age of 15 years (1), and if the rate of malignant transformation of

OLP is set at 1% in a mean period of five years (which is the average of the rates seen in the reviewed studies and is equivalent to an annual rate of 0.2%), then ten to twenty patients per 100,000 people would develop oral cancer in a period of five years, which results in an annual incidence of oral cancer on the basis of malignant transformation of OLP only, of two to four per 100,000 people. This would mean that in many parts of the world all oral cancer cases would develop on the basis of OLP only, which is extremely unlikely. As a matter of fact, in our group of 724 patients with oral squamous cell carcinoma only two patients were observed with the simultaneous presence of OLP, which was either of coincidental or causal significance (17). In other words, in our series less than 1% of all oral cancers might have developed on the basis of OLP. Therefore, either the annual malignant transformation rate or the prevalence figure of OLP needs adjustment. Inasmuch as the prevalence figure of OLP of 1% to 2% that was used in this calculation is based on a reliable demographic study involving a large West-European (Swedish) population of more than 20,000 subjects (1), it seems likely that the annual malignant transformation rate of OLP is much lower than the presently used figure of 0.2%. The high malignant transformation rates found in the studies that yielded this figure might be due to 1) the occurrence of malignant transformations that were in fact not cases of OLP and/or to 2) the highly selected populations (i.e., the types of subjects most often referred for evaluation and treatment) used in those studies. A recent preliminary report from Sweden where OLP lesions in a general population have been followed for twenty years indicates that the premalignant potential of the investigated OLP lesions is very low (36). If this is true, one may raise the question whether such a small percentage still qualifies for the use of the term premalignant or potentially malignant.

Our review of the literature does not argue against the validity of some of the previous reported studies; rather, it underlines the need to be more specific when reporting this type of material. Therefore, we would first like to call for future publications on this subject with complete, detailed documentary data. Second, we wish to stress the need for uniformly accepted criteria to establish a firm diagnosis of OLP. Only when such diagnostic criteria are available will it be possible to conduct long-term prospective studies with well-defined protocols for the collecting of data. As long as such data are unavailable, the premalignant nature of OLP should be regarded as uncertain.

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CHAPTER 2

INTEROBSERVER AND INTRAOBSERVER VARIABILITY IN THE HISTOLOGIC ASSESSMENT OF ORAL LICHEN PLANUS

E.H. van der Meij[1]
J. Reibel[2]
P.J. Slootweg[3]
J.E. van der Wal[1]
W.F.B. de Jong[1]
I. van der Waal[1]

1 Department of Oral and Maxillofacial Surgery/Oral Pathology, Academic Centre for Dentistry Amsterdam (ACTA)/Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

2 Department of Oral Pathology and Medicine, University of Copenhagen, Copenhagen, Denmark

3 Department of Pathology, Utrecht Medical Centre, Utrecht, The Netherlands

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Abstract

The purpose of this study was to evaluate interobserver and intraobserver variability in the histopathological assessment of OLP, since this may influence the outcome of studies on epidemiology, treatment and prognosis. Five oral pathologists examined 60 microscopic slides, not being informed about the original histopathological assessment. Fourty-five of the cases had been originally signed out as OLP; the remaining 15 cases represented a mixture of other oral white lesions. No clinical information or patient data were provided with the cases. Each reviewing pathologist was asked to apply the WHO definition of OLP and to categorize each case as either: 1) evident OLP, 2) compatible with OLP, or 3) no histological support for OLP. After two months, each of the five reviewing pathologists were given 45 slides that were randomly retrieved from the original 60. Interobserver and intraobserver variability were assessed by calculation of unweighted kappa statistics. Interobserver agreement varied from 0.20 (poor) to 0.51 (moderate), while the intraobserver agreement varied from 0.50 (moderate) to 0.67 (substantial). Histopathological assessment of OLP, based on the available WHO definition, is a rather subjective and insufficiently reproducible process. Stricter diagnostic criteria are required in order to obtain a more reproducible diagnosis of OLP.

Introduction

OLP is a syndrome diagnosis, i.e., based on the presence of several clinical and histopathological criteria. Thus, the diagnostic approach is best described as the method of pattern recognition both clinically and histologically. The purpose of the diagnostic process is, of course, to make it possible to decide on treatment and prognosis. For instance, studies on the possible premalignant character of OLP are less meaningful and may even be confusing and inconsistent if a precise diagnosis of OLP cannot be made.

A histopathological definition of OLP was formulated by the WHO in 1978 as follows (1): “The histopathologic features of OLP are characteristic. There is usually a keratinized layer, and this may be either ortho- or parakeratinized. If keratinization is normally found at the affected site, then the keratinized layer is thickened. If the site is normally nonkeratinized (for example, buccal mucosa), the keratinized layer in the

lichen planus lesion may be very thin; if there is normally a stratum granulosum this will be thickened. If there is normally no stratum granulosum, then granular cells may be present in small numbers. The 'saw-tooth' appearance of the rete processes that is a common feature of skin lesions is less frequently seen in the oral mucosa. The thickness of the epithelium varies, and atrophy is often seen. Civatte (colloid) bodies may be present in the region of the basal-cell layer, lying either in the epithelium or within the superficial part of the connective tissue. These are rounded or lobulated acidophilic structures which sometimes contain a pyknotic nucleus or nuclear fragments. The changes in the basal-cell layer often include 'liquefaction degeneration', and there may be a narrow band of eosinophilic material in the position of the basement membrane. There is a well-defined zone of cellular infiltration that is confined to the superficial part of the connective tissue (lamina propria), and the infiltrate consists mainly of lymphocytes except in the vicinity of an erosion." At first glance, the histopathological definition of OLP seems to result in a well-described entity. However, it is known that the process by which a pathologist makes a diagnosis is inherently subjective (2-4). Factors as diverse as information provided by the clinician, and the training and experience of the pathologist may play a part in determining the final 'sign-out' diagnosis.

The aim of this study was to evaluate interobserver and intraobserver variability in the histopathological diagnosis of OLP, based on the WHO definition. Furthermore, we investigated whether interobserver variability between pathologists of the same department differed from the variability between pathologists from different departments.

Patients and methods

Five oral pathologists (JRE, PSL, JWA, WJO and IWA), three from the Vrije Universiteit Medical Centre, Amsterdam, one from the University of Copenhagen and one from the Utrecht Medical Centre were recruited to be examiners for this study. Each pathologist was given 60 microscopic slides that were labeled only with a number. No clinical information or patient data were given to the pathologists. The 60 slides were selected by an investigator (EME) who did not participate as one of the reviewing pathologists. The slides were obtained from the files of the Department of Oral and Maxillofacial Surgery and Oral Pathology of the

Vrije Universiteit Medical Centre, Amsterdam. Fourty-five of the cases had been originally signed out as OLP; the remaining 15 cases represented a mixture of other oral white lesions. The reviewing pathologists were informed that their slides represented a mixture of oral white lesions, including OLP, but were unaware of the percentage of each diagnosis. They knew that their judgement would be compared with those of the others, but they had no calibration exercises beforehand. Each reviewing pathologist was asked to apply the aforementioned WHO definition of OLP from 1978 (1) and to categorize each case as either: 1) evident OLP, 2) compatible with OLP, or 3) no histologic support for OLP.

Two months after their diagnoses were returned, each of the five reviewing pathologists was given 45 slides randomly retrieved from the original 60. The reviewing pathologists were informed that these slides came from the original 60 cases but, again, no clinical information was provided.

Interobserver and intraobserver variability were tested. The scores ('evident OLP', 'compatible with OLP', and 'no histologic support for OLP') were placed in 3×3 tables. The observed agreement rates were calculated as the sum of the diagonal cells in a given table in relation to the total number of observations. The expected chance agreement rates in relation to the diagonal were calculated as a general calculation of probability. The expected values are the values which would be the result if the scoring was purely at random. The interobserver and intraobserver variability were assessed by calculation of unweighted kappa statistics (5). Kappa score is commonly used to evaluate reliability of paired agreements against pure chance agreement (range 0 (random agreement) to 1 (perfect agreement)) (2,5). Kappa (κ) is calculated from the following: $\kappa = (X-Y)/(Z-Y)$, where X is the observed agreement, Y the expected chance agreement, and Z the perfect agreement. The following grading of kappa values was used: $\kappa < 0.4$ = poor agreement, $\kappa \geq 0.4$ and < 0.6 = moderate agreement, $\kappa \geq 0.6$ and < 0.8 = substantial agreement, $\kappa \geq 0.80$ = good agreement.

Besides, category 1 ('evident OLP') and category 2 ('compatible with OLP') were taken together and compared with category 3 ('no histologic support for OLP'). Scores were placed in 2×2 tables and unweighted kappa statistics were calculated in the same manner as described above.

Finally, interobserver agreement rates between pathologists from the same department were compared with interobserver agreement rates

between pathologists from different departments using Student's *t*-statistics.

Results

Interobserver and intraobserver agreement rates are summarized in Table 2.1 and 2.2. Interobserver agreements defined by kappa varied from 0.20 (poor) to 0.51 (moderate), while intraobserver agreements varied from

Table 2.1.
Interobserver and intraobserver agreement rates (category 1, versus 2, versus 3)

Pathologist	**A**	**B**	**C**	**D**	**E**
A	**0.67**	0.58	0.63	0.57	0.57
B	-	**0.73**	0.67	0.62	0.62
C	-	-	**0.78**	0.62	0.60
D	-	-	-	**0.76**	0.52
E	-	-	-	-	**0.73**

Table 2.2.
Interobserver and intraobserver agreement rates (category (1+2), versus 3)

Pathologist	**A**	**B**	**C**	**D**	**E**
A	**0.80**	0.82	0.77	0.78	0.78
B	-	**0.87**	0.78	0.83	0.77
C	-	-	**0.91**	0.78	0.78
D	-	-	-	**0.80**	0.75
E	-	-	-	-	**0.96**

Results printed **boldface** represent the intraobserver agreement rates. Results printed normal typeface represent the interobserver agreement rates.

category 1) = 'evident OLP'
category 2) = 'compatible with OLP'
category 3) = 'no histologic support for OLP'

Table 2.3.
Interobserver and intraobserver agreements defined by kappa (category 1, versus 2, versus 3)

Pathologist	**A**	**B**	**C**	**D**	**E**
A	**0.50 (moderate)**	0.37 (poor)	0.43 (moderate)	0.34 (poor)	0.35 (poor)
B	-	**0.60 (substantial)**	0.51 (moderate)	0.43 (moderate)	0.42 (moderate)
C	-	-	**0.67 (substantial)**	0.42 (moderate)	0.40 (moderate)
D	-	-	-	**0.61 (substantial)**	0.20 (poor)
E	-	-	-	-	**0.60 (substantial)**

Table 2.4.
Interobserver and intraobserver agreements defined by kappa (category (1+2), versus 3)

Pathologist	**A**	**B**	**C**	**D**	**E**
A	**0.60 (substantial)**	0.62 (substantial)	0.52 (moderate)	0.56 (moderate)	0.54 (moderate)
B	-	**0.71 (substantial)**	0.52 (moderate)	0.65 (substantial)	0.49 (moderate)
C	-	-	**0.80 (good)**	0.56 (moderate)	0.53 (moderate)
D	-	-	-	**0.60 (substantial)**	0.50 (moderate)
E	-	-	-	-	**0.90 (good)**

Results printed **boldface** represent the intraobserver agreements. Results printed normal typeface represent the interobserver agreements.

category 1) = ‘evident OLP’
category 2) = ‘compatible with OLP’
category 3) = ‘no histologic support for OLP’

0.50 (moderate) to 0.67 (substantial) (Table 2.3). When category 1 ('evident OLP') and category 2 ('compatible with OLP') were taken together and compared with category 3 ('no histologic support for OLP') interobserver and intraobserver agreements were somewhat higher (Table 2.4).

When comparing interobserver agreement rates between pathologists from the same department with interobserver agreement rates between pathologists from different departments, no statistical significant differences were found.

Discussion

In 1995, Abbey et al. stated that the process by which a pathologist makes a diagnosis is to some extent a subjective process (2); their statement was based on a study of the interobserver and intraobserver variability in the histological assessment of oral epithelial dysplasia. Similar experience within the same diagnostic group has been reported by others (6,7). Although it has been suggested that difficulties similar to the ones found with oral epithelial dysplasia may play a role in diagnosing OLP, no studies have been undertaken to prove this (8,9).

Our results demonstrate poor to moderate agreement among pathologists diagnosing OLP, suggesting the existence of subjectivity in interpreting the WHO definition of OLP. We used this definition as a starting-point because this is probably the most commonly accepted histopathological definition of OLP. A variety of histopathological features are incorporated in this definition; subjectivity in the interpretation of this definition is probably caused by uncertainty that exists about the value of each of these histopathological features in reaching a final histopathological diagnosis of OLP. For instance, some pathologists may believe that a superficial bandlike inflammatory infiltrate is an important feature of OLP, while others may pay more attention to the presence of Civatte bodies. In 1985, Krutchkoff et al. proposed a histopathological subclassification of oral lichenoid lesions (9). In their set of criteria a distinction was made between important, requisite features and less important, additional features. However, the results of validation of these criteria have not yet been published.

When intraobserver variability in the second phase of the study was evaluated, agreement rates appeared to be significantly higher than interobserver agreements, being between moderate and substantial. This

finding suggests that pathologists have their own interpretation of the histopathological criteria of OLP, often being different from those of other pathologists.

In our study no differences in interobserver agreements between pathologists from the same department and between pathologists from different departments were observed. However, one might expect that pathologists from the same department, having daily discussions on several diagnostic problems, would do better in such a test. This again suggests that interobserver variability is due to individual differences rather than to other factors. A similar finding has been reported by Karabulut et al., who investigated the extent of agreement in grading epithelial dysplasia between pathologists with the same or different educational background (6). They, too, concluded that interobserver variability is probably based on individual differences rather than on factors such as education.

When category 1 and category 2 were taken together, interobserver agreement rates increased but were still not higher than moderate to substantial. This means that there were a considerable number of cases that some pathologists interpreted as being 'evident of OLP' or 'compatible with OLP', while others classified those as being of 'no histological support for OLP'.

The reviewing pathologists were not aware of the clinical presentation of the lesions, as this might have influenced their diagnostic decision-making. On the other hand, in a somewhat similar study regarding the presence and degree of epithelial dysplasia, the inclusion of clinical information did not improve the interobserver agreement rate in the diagnosis of oral epithelial dysplasia (10).

Concluding that diagnosing OLP histopathologically is a rather subjective and poorly reproducible process has important consequences. For example, reported studies of the possible premalignant character of OLP might have included lesions with diverse histological characteristics that may not represent the same disease entity. Improving the diagnostic criteria is, indeed, of utmost importance.

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CHAPTER 3

INTEROBSERVER AND INTRAOBSERVER VARIABILITY IN THE CLINICAL ASSESSMENT OF ORAL LICHEN PLANUS

E.H. van der Meij[1]
K.P. Schepman[2]
D.R. Plonait[3]
T. Axéll[4]
I. van der Waal[1]

1 Department of Oral and Maxillofacial Surgery/Oral Pathology, Academic Centre for Dentistry Amsterdam (ACTA)/Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

2 Department of Oral and Maxillofacial Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

3 Department of Oral Surgery and Dental Radiology, Charité, Campus Virchow, Faculty of Medicine, Humboldt University, Berlin, Germany

4 Section of Gerodontology, Faculty of Dentistry, University of Oslo, Norway

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Abstract

In 1978, a clinical definition of OLP was formulated by the WHO. To date, the validation results of this clinical definition have not been published. The aim of this study was to evaluate interobserver and intraobserver variability in the clinical assessment of OLP.

Four clinicians examined a set of 159 clinical pictures of a white lesion in a group of 60 patients. Each reviewing examiner was asked to apply the WHO definition of OLP from 1978, and to categorize each case as either: 1) diagnostic of OLP, 2) other definable lesion, or 3) leukoplakia. After three months, each of the four reviewing clinicians was given the clinical pictures of 45 randomly retrieved cases from the original 60. Interobserver and intraobserver variability were assessed by calculation of unweighted kappa statistics.

Interobserver agreement varied from 0.43 (moderate) to 0.77 (substantial), while the intraobserver agreement varied from 0.62 (substantial) to 0.92 (good).

Although the clinical WHO definition of OLP seems to be more reproducible than the histopathological one, there is still a significant amount of subjectivity in using this definition. A set of clinical and histopathological diagnostic criteria with good interobserver and intraobserver agreements (kappa values > 0.8) is important in enabling reproducible and reliable studies on several aspects of OLP to be performed.

Introduction

OLP is a syndrome diagnosis, i.e., based on the presence of several clinical and histopathological criteria. Thus, the diagnostic approach is best described as a method of pattern recognition both clinically and histologically. The purpose of the diagnostic process is, of course, to make it possible to decide on treatment and prognosis. For instance, studies on the possible premalignant character of OLP are less meaningful, and may even be confusing and inconsistent if a precise diagnosis of OLP cannot be made (1).

In 1978, a clinical definition of OLP was formulated by the WHO as follows (2): “OLP commonly affects the oral mucosa, and lesions may occur in the mouth in the absence of skin lesions. Mucosal lesions are usually multiple and often have a symmetrical distribution. They

commonly take the form of minute white papules which gradually enlarge and coalesce to form either a reticular, annular, or plaque pattern. A characteristic feature is the presence of slender white lines (Wickham's striae) radiating from the papules. In the reticular form there is a lacelike network of slightly raised gray-white lines, often interspersed with papules or rings. The plaque form may be difficult to distinguish from leukoplakia, but in OLP there is usually no change in the flexibility of the affected mucosa. In some patients the lesions are atrophic, with or without erosions. Oral lesions of lichen planus may also include bullae, but these are rare." A variety of clinical characteristics are incorporated into this definition, such as morphological features, anatomical location and the presence or absence of symmetrical/bilateral appearance. To date, the validation results of this clinical definition have not been published.

The aim of this study was to evaluate interobserver and intraobserver variability in the clinical assessment of OLP, based on the available WHO definition. In addition, we evaluated whether the assessment of a clinical diagnosis of OLP is based mainly on morphological aspects of the lesion, or also on other clinical characteristics, such as the anatomical location, the presence or absence of symmetrical and/or bilateral appearance.

Patients and methods

Four clinicians (KSC, DPL, TAX, IWA), from three different universities were recruited as examiners for this study. Two examiners had approximately 10 years of clinical experience (KSC, DPL), while the other two had more than 25 years of clinical experience (TAX, IWA). In the first session, each clinician was given 60 clinical pictures. Each picture showed an oral white lesion from one anatomical site of one patient. No further clinical information or patient data were given to the examiner. The 60 pictures were selected by an investigator (EME) who did not participate as one of the reviewing examiners and represented the same 60 cases as used in Chapter 2 (1). The reviewing clinicians were informed that their pictures represented a mixture of oral white lesions, including OLP, but were unaware of the percentage of each diagnosis. They were fully aware that their judgement would be compared to others, and had no calibration exercises beforehand. Each reviewing examiner was asked to apply the aforementioned WHO definition of OLP from 1978 (2) and the Uppsala definition of oral leukoplakia from 1994 (3),

and to categorize each case as either: 1) diagnostic of OLP, 2) other definable lesion, or 3) leukoplakia.

In the second session, directly after the first one, each of the four reviewing clinicians were given a complete set of 159 clinical pictures including every anatomical site with a white lesion of the original group of 60 patients, to assess the impact of clinical characteristics other than the morphology of the OLP lesion on clinical diagnosing. Each reviewing examiner was again asked to diagnose the 60 cases in the same manner as described in session one.

Three months after their diagnoses were returned, each of the four reviewing examiners were given a complete set of clinical pictures (including every anatomical site with a white lesion) from 45 cases randomly retrieved from the original 60 (session 3). The reviewing examiners were informed that these pictures came from the original 60 cases. Assessment of diagnosis of these 45 cases took place as described in session one and two.

Interobserver and intraobserver variability were tested using the data from session two and three. The scores ('clinically OLP', 'other definable lesion', and 'leukoplakia') were placed in 3×3 tables. The observed agreement rates were calculated as the sum of the diagonal cells in a given table, in relation to the total number of observations. The expected agreement rates by chance, in relation to the diagonal, were calculated as a general calculation of probability. The expected values are those that would be obtained if the scoring was purely random. The interobserver and intraobserver variability was assessed by calculation of unweighted kappa statistics (4). A kappa score is commonly used to evaluate reliability of paired agreements compared to those obtained by pure chance (range 0 (random agreement) to 1 (perfect agreement)) (4,5). Kappa (κ) is calculated from the following: $\kappa = (X-Y)/(Z-Y)$, where X is the observed agreement, Y the expected chance agreement, and Z the perfect agreement. The following grading of kappa values was used: $\kappa < 0.4$ = poor agreement, $\kappa \geq 0.4$ and < 0.6 = moderate agreement, $\kappa \geq 0.6$ and < 0.8 = substantial agreement, $\kappa \geq 0.80$ = good agreement.

Finally, the impact of clinical characteristics other than the morphological features of the OLP lesion, on clinical diagnosing was assessed by calculating intraobserver variability using data from sessions one and two. Unweighted kappa statistics were calculated in the same manner as described above.

Table 3.1.
Interobserver and intraobserver agreement rates

Clinician	**A**	**B**	**C**	**D**
A	**0.96**	0.82	0.88	0.81
B	-	**0.91**	0.77	0.67
C	-	-	**0.89**	0.76
D	-	-	-	**0.76**

Results printed **boldface** represent the intraobserver agreement rates. Results printed normal typeface represent the interobserver agreement rates.

Table 3.2.
Interobserver and intraobserver agreements defined by kappa

Clinician	**A**	**B**	**C**	**D**
A	**0.92 (good)**	0.68 (substantial)	0.77 (substantial)	0.65 (substantial)
B	-	**0.85 (good)**	0.57 (moderate)	0.43 (moderate)
C	-	-	**0.76 (substantial)**	0.52 (moderate)
D	-	-	-	**0.62 (substantial)**

Results printed **boldface** represent the intraobserver agreements. Results printed normal typeface represent the interobserver agreements.

Table 3.3.
Impact of clinical characteristics other than morphological aspects of the OLP lesion on clinical diagnosing: intraobserver agreement rates

Clinician	**A**	**B**	**C**	**D**
	0.90	0.75	0.87	0.85

Table 3.4.
Impact of clinical characteristics other than morphological aspects of the OLP lesion on clinical diagnosing: intraobserver agreements defined by kappa

Clinician	**A**	**B**	**C**	**D**
	0.82 (good)	0.60 (substantial)	0.69 (substantial)	0.72 (substantial)

Results

Interobserver and intraobserver agreement rates are summarised in Table 3.1. Interobserver agreements, defined by kappa, varied from 0.43 (moderate) to 0.77 (substantial), while intraobserver agreements varied from 0.62 (substantial) to 0.92 (good) (Table 3.2).

The impact of clinical characteristics, other than morphological aspects of the OLP lesion, on clinical diagnosing, expressed as intraobserver agreement rates is shown in Table 3.3. The accompanying intraobserver agreements, defined by kappa, varied from 0.60 (moderate) to 0.82 (good) (Table 3.4).

Discussion

In our previous study, described in Chapter 2, evaluating interobserver and intraobserver variability in the histopathological assessment of OLP, interobserver agreement, defined by kappa, varied from 0.20 (poor) to 0.51 (moderate) (1). Results of the present study demonstrate better agreement in the clinical assessment of OLP with kappa values varying from 0.43 (moderate) to 0.77 (substantial). Although the clinical WHO definition of OLP seems to be more reproducible than the histopathological one, some subjectivity in interpreting this definition still remains.

Intraobserver agreement rates were good to substantial an appeared to be significantly higher than interobserver agreement rates. A similar phenomenon occurred in our previous study, where interobserver and intraobserver variability was evaluated in the histopathological assessment of OLP (1). Clinicians, as well as pathologists, seem to have

their own interpretation of the clinical and histopathological definition of OLP, and this is often different from other observers.

Calculation of intraobserver variability, using data from sessions one and two, was performed to evaluate whether the assessment of a clinical diagnosis of OLP is mainly based on morphological aspects of the lesion or also on other clinical characteristics, such as the anatomical location, the presence or absence of symmetrical and/or bilateral appearance. Kappa values varied from 0.60 (substantial) to 0.82 (good) meaning there was a significant impact of these other clinical characteristics on clinical decision making. For example, oral lesions of lupus erythematosus (systemic or chronic discoid type) can exhibit clinical morphological features that are strikingly similar to those of OLP. However, the anatomical location and the presence of symmetrical and/or bilateral appearance can help distinguish between lupus-associated disorders and the pattern recognised as OLP (6). A revised clinical definition of OLP incorporating only morphological features would therefore be insufficient and, thus, other clinical characteristics should also be included.

Subjectivity in interpreting the clinical WHO definition of OLP may be partially due to the lack of consensus on the use of the terms OLP and OLL. The latter includes lesions such as drug-induced OLL and amalgam-associated OLL. For example, amalgam-associated OLL present with similar clinical characteristics to OLP, and the two lesions are only distinguished by the degree of involvement of the oral mucosa (7,8). Amalgam-associated OLL are confined to areas of frequent contacts with restorations of dental amalgam, while OLP also occurs in other regions of the oral mucosa. Attempts that have been made to use histopathological examination supplemented with immunohistochemistry have failed to detect specific differences in amalgam-associated OLL and OLP lesions (9). Some clinicians include OLL under the term OLP while others consider OLL as a separate definable entity. A revised clinical definition of OLP should provide a clear distinction between OLP and OLL.

A set of clinical and histopathological diagnostic criteria, with good interobserver and intraobserver agreements (kappa values > 0.8), is of utmost importance in enabling reproducible and reliable studies on several aspects of OLP to be performed.

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CHAPTER 4

LACK OF CLINICOPATHOLOGICAL CORRELATION IN THE DIAGNOSIS OF ORAL LICHEN PLANUS BASED ON THE PRESENTLY AVAILABLE DIAGNOSTIC CRITERIA AND SUGGESTIONS FOR MODIFICATIONS

E.H. van der Meij[1]
I. van der Waal[1]

1 Department of Oral and Maxillofacial Surgery/Oral Pathology, Academic Centre for Dentistry Amsterdam (ACTA)/Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

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Abstract

Confirmation of a clinical diagnosis of OLP by means of histopathological study of a biopsy specimen is generally advised. However, hardly any data exist about the correlation between clinical and histopathological diagnoses of OLP. The aim of the present investigation was to study the correlation between the clinical and histopathological assessment of OLP, and to propose diagnostic refinements, if appropriate.

Clinical and histopathological data from Chapter 2 and 3 were used for this purpose. The number of clinical cases of which all clinicians agreed, as well as the number of microscopic slides of which all reviewing pathologists agreed, were calculated and compared with each other in order to assess the clinicopathological correlation.

In 42% of the cases of which all clinicians agreed about the clinical diagnosis, being diagnostic of OLP, there appeared to be no consensus on the histopathological diagnosis. Conversely, in 50% of the cases of which all pathologists agreed about the histopathological diagnosis, being diagnostic of OLP, there was a lack of consensus on the clinical diagnosis.

Based on the findings of the present study there appears to be a lack of clinicopathological correlation in the diagnostic assessment of OLP. We therefore propose a set of revised diagnostic criteria of OLP and oral lichenoid lesions, based on the WHO definition of OLP, including clinical as well as histopathological aspects.

Introduction

As OLP is regarded to be a clinicopathological diagnosis, i.e., based on a combination of clinical and histopathological criteria, confirmation of a clinical diagnosis of OLP by histopathological study of a biopsy specimen is generally advised (1). Onofre et al. studied the correlation between clinical and histopathological diagnoses in 45 patients with leukoplakia and OLP and found a clinicopathological discrepancy in a quarter of these lesions (2). To date, no other data exist about the degree of correlation between clinical and histopathological diagnoses of OLP.

The aim of the present investigation was to study the correlation between the clinical and histopathological assessment of OLP. Clinical and histopathological data from Chapter 2 and 3 were used for this purpose (3,4).

Patients and Methods

In a Chapter 2 the interobserver and intraobserver variability in the histologic assessment of OLP were evaluated (3). Five reviewing pathologists were asked to apply the histopathological definition of OLP, as formulated by the WHO in 1978 (5), and to categorize a total number of 60 microscopic slides as either: 1) evident OLP, 2) compatible with OLP, or 3) no histologic support for OLP. In Chapter 3, the interobserver and intraobserver variability in the clinical assessment of OLP were studied using clinical pictures of 60 cases, representing the same cases as used in Chapter 2 (4). Four clinicians categorized each case as either: 1) diagnostic of OLP, 2) other definable lesion, or 3) leukoplakia, applying the clinical WHO definition of OLP (5). For further details of these studies see also the 'patients and methods' section of Chapter 2 and 3 (3,4).

To assess the degree of clinicopathological correlation of OLP, data of the aforementioned clinical and histopathological study were compared. The number of clinical cases of which all clinicians agreed were calculated. For this purpose, category 2 ('other definable lesion') and category 3 ('leukoplakia') were taken together. The number of microscopic slides of which all reviewing pathologists agreed were calculated as well, taking category 1 ('evident OLP') and category 2 ('compatible with OLP') together. Scores of clinical and histopathological data were placed in a 3×3 table.

Results

In 8 out of 19 cases of which all clinicians agreed that the clinical picture was diagnostic of OLP, there was no complete agreement of the histopathological diagnosis in 7 cases, while all pathologists unanimously agreed that there was no histologic support for OLP in 1 case (figure 4.1a and 4.1b).

Conversely, in 22 cases of which all pathologists agreed about the histopathological diagnosis, being either 'evident OLP' or 'compatible with OLP', 10 lacked consensus about the clinical diagnosis (figure 4.2a and 4.2b), and in one case the clinicians all agreed that there were no clinical characteristics of OLP at all.

The results of comparison of the clinical and histopathological data are summarized in Table 4.1.

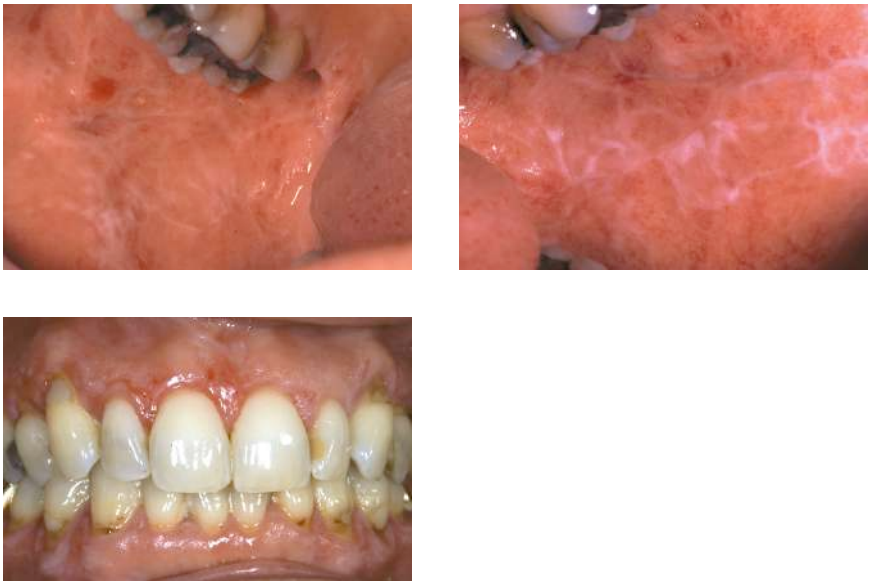

Figure 4.1a. Clinical slides of a case of which all reviewing clinicians agreed about the clinical diagnosis being 'diagnostic of OLP'.

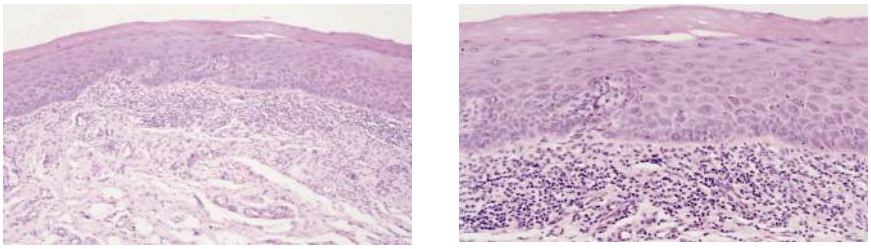

Figure 4.1b. Microscopic slide of the same patient in figure 4.1a. There was no consensus about the histologic diagnosis; three pathologists assessed the case as 'compatible with OLP', one pathologist as 'evident OLP', and one pathologist as 'no histologic support for OLP'.

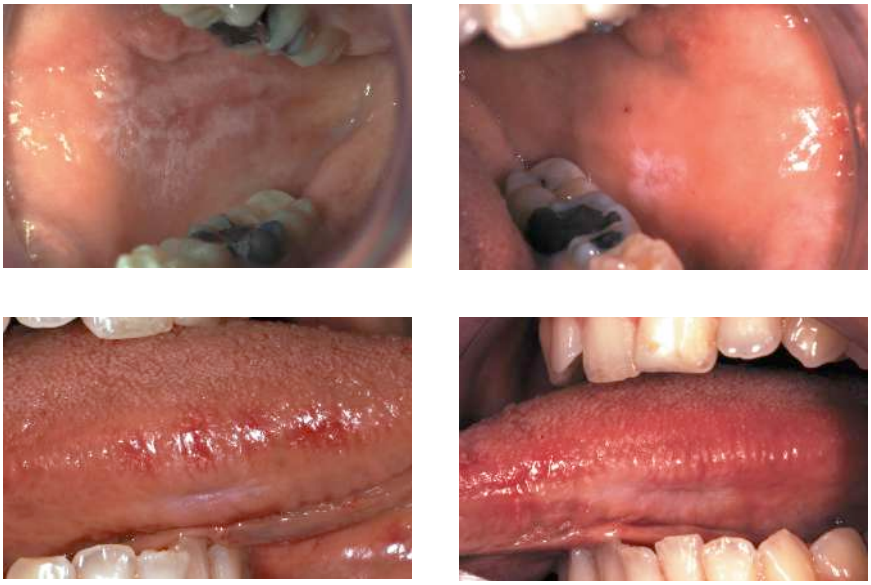

Figure 4.2a. Clinical slides of a case of which there was no consensus about the clinical diagnosis. Three clinicians assessed the case as 'evident OLP', and one clinician as 'other definable lesion'.

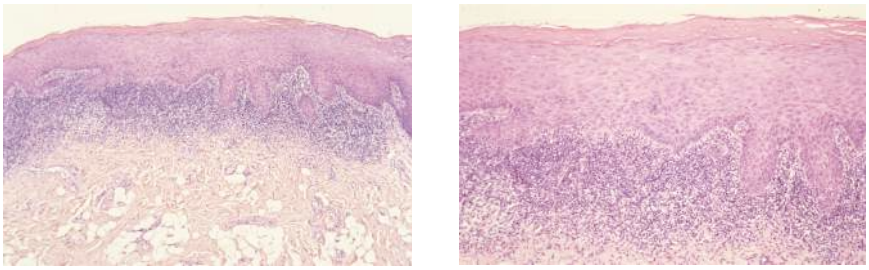

Figure 4.2b. All reviewing pathologists agreed about the histologic diagnosis being 'evident OLP'.

Table 4.1.
Comparison of the outcome of clinical and histopathological assessment of OLP

		histologic assessment[2]			
		all agree 1 or 2	**all agree 3**	**no agreement**	**total**
clinical assessment[1]	**all agree 1**	11	1	7	**19**
	all agree 2 or 3	1	7	4	**12**
	no agreement	10	3	16	**29**
	total	**22**	**11**	**27**	**60**

[1]clinical assessment: category 1) = 'diagnostic of OLP'
category 2) = 'other definable lesion'
category 3) = 'leukoplakia'

[2]histologic assessment: category 1) = 'evident OLP'
category 2) = 'compatible with OLP'
category 3) = 'no histologic support for OLP'

Discussion

A clinical and histopathological definition of OLP was formulated by the WHO in 1978 (5). Ever since, this definition has been used in the diagnostic assessment of OLP, and has especially been applied as 'golden standard' in the inclusion of patients in studies focusing on several aspects of OLP, including those on the possible premalignant character of OLP. Validation of this definition has never been performed.

In Chapter 2 and 3, the interobserver and intraobserver variability in the clinical and histologic assessment of OLP, based on this WHO definition, have been described (3,4). It was demonstrated that interobserver agreement in the clinical and histologic assessment of OLP, defined by kappa, varied from moderate to substantial, and from poor to moderate, respectively. Intraobserver agreement appeared to be significantly better in both studies. A call for stricter diagnostic criteria in order to obtain a more reproducible diagnosis of OLP was therefore made. Such revised criteria should enable us to achieve consensus on the diagnostic assessment of OLP.

Comparison of the results of clinical and histopathological assessment of OLP in the present analysis shows lack of correlation. In

42% of the cases (8 out of 19) of which all clinicians agreed about the clinical diagnosis, there appeared to be no consensus on the histopathological diagnosis. Conversely, in only 50% of the cases (11 out of 22) of which all pathologists agreed about the histopathological diagnosis, all clinicians agreed about the clinical diagnosis, being 'diagnostic of OLP'. How might the lack of clinicopathological correlation be explained? Firstly, the choice of selecting the most appropriate area for biopsy might play a role. Gynther et al. reported on the advantages of the application of direct oral microscopy in selecting the representative site for a biopsy compared with clinical examination alone (6). Secondly, the lack of clinicopathological correlation might partially be caused by the study design. The reviewing pathologists were not aware of the clinical presentation of the lesions, as this might have influenced their diagnostic decision-making. On the other hand, in a somewhat similar study regarding the presence and degree of epithelial dysplasia, the inclusion of clinical information did not improve the interobserver agreement rate in the diagnosis of oral epithelial dysplasia (7). Finally, the lack of clinical diagnostic criteria in order to differentiate oral lichenoid lesions (e.g. drug or amalgam-associated) from 'idiopathic' OLP might be partially responsible for the lack of clinicopathological correlation.

Lack of clinicopathological correlation in the diagnosis of OLP means that we cannot rely on a clinical or a histopathological diagnosis alone. We therefore propose a set of revised diagnostic criteria of OLP and OLL, based on the WHO definition of OLP, including clinical as well as histopathological aspects. The modified definition of the WHO has been summarized in table 4.2.

The main reason for development of the presently proposed diagnostic criteria is to enable the researcher to perform reproducible studies on several aspects of OLP and OLL, and by doing so, to reduce or possibly eliminate confusion, e.g., about the possible premalignant character of OLP and OLL. Use of these diagnostic criteria should eliminate individual diagnostic variation based upon training, experience, or idiosyncratic bias of the clinician and the pathologist. We do realize that application of these criteria will exclude a number of patients who actually may have the disease, but who do not meet the strict criteria.

In the description of the proposed criteria no attention has been paid to amalgam-associated lesions and drug induced lesions. No distinction

Table 4.2.
Proposal for a set of modified WHO diagnostic criteria of oral lichen planus (OLP) and oral lichenoid lesions (OLL)

CLINICAL CRITERIA

- presence of bilateral, more or less symmetrical lesions
- presence of a lacelike network of slightly raised gray-white lines (reticular pattern)
- erosive, atrophic, bullous and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa

In all other lesions that resemble OLP but not complete the aforementioned criteria the term 'clinically compatible with' should be used.

HISTOPATHOLOGICAL CRITERIA

- presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
- signs of 'liquefaction degeneration' in the basal cell layer
- absence of epithelial dysplasia

When the histopathological features are less obvious, the term 'histopathologically compatible with' should be used.

FINAL DIAGNOSIS OLP OR OLL

To achieve a final diagnosis clinical as well as histopathological criteria should be included.

OLP. A diagnosis of OLP requires fulfillment of both clinical and histopathological criteria.
OLL. The term OLL will be used under the following conditions:

1) clinically typical of OLP but histopathologically only 'compatible with' OLP,
2) histopathologically typical of OLP but clinically only 'compatible with' OLP
3) clinically 'compatible with' OLP and histo- pathologically 'compatible with' OLP.

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can be made between these lesions and OLP on either clinical or histopathological grounds and, to date, no additional diagnostic tools exist. Applying the proposed criteria, those lesions will probably be categorized as OLL.

In 1985, Krutchkoff and Eisenberg proposed a system of histopathological subclassification of OLP and OLL, and introduced the term 'lichenoid dysplasia (LD)' as a distinct histopathological entity (8). LD was defined as a lesion that histopathologically revealed characteristics of OLP and the additional presence of dysplastic features within the overlying epithelium. However, the validation of this system of subclassification has not been published yet. To avoid confusion about this terminology, we propose to regard the presence of epithelial dysplasia as an exclusion criterion for the histopathological diagnosis of OLP. In contrast with Krutchkoff and Eisenberg's system we would like to emphasize that a diagnosis of OLP should not be assessed on the histopathological picture alone, but should also be based on distinct clinical criteria. Histopathologically typical OLP does in a substantial percentage not correlate with a clinical typical appearance.

Although several molecular biological markers have been suggested to be useful as an additional diagnostic tool in diagnosing OLP, there seems not to be enough scientific evidence yet to apply those as a 'golden standard' (9-13). Direct immunofluorescent techniques have also been described as additional tool in the diagnostic assessment of OLP (14-20). Although some immunofluorescent findings are found to be highly characteristic of OLP, such as the presence of fibrin deposition at the mucosal-submucosal junction, within vessels and cytoid bodies, these findings seem to lack specificity. Direct immunofluorescent tests do not represent a definite additional diagnostic criterion for OLP, but may occasionally be additional supportive markers in the diagnosis of the disease.

In conclusion, based on the findings of the present study, there appears to be a lack of clinicopathological correlation in the diagnostic assessment of OLP. The presently proposed, modified WHO definition of OLP and OLL, including clinical as well as histopathological criteria, might enable the researcher to perform reproducible studies on several aspects of OLP and OLL, and by doing so, might reduce or possibly eliminate confusion, e.g., about the possible premalignant character of OLP and OLL. Before the proposed criteria can be applied, validation is of utmost importance. In the near future those criteria might be replaced by or added with molecular biological aspects of OLP.

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CHAPTER 5

THE POSSIBLE PREMALIGNANT CHARACTER OF ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS; A PROSPECTIVE STUDY

E.H. van der Meij[1]
K.P. Schepman[2]
I. van der Waal[1]

1 Department of Oral and Maxillofacial Surgery/Oral Pathology, Academic Centre for Dentistry Amsterdam (ACTA)/Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

2 Department of Oral and Maxillofacial Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

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Abstract

Possible malignant transformation of OLP is the subject of an ongoing and controversial discussion in the literature. The main criticism on studies on this subject consists of lack of sufficient data to support the initial diagnosis of OLP in cases that finally developed into a squamous cell carcinoma. The present report describes the possible premalignant character of OLP and OLL of a prospectively followed cohort of patients with detailed documentary data applying the proposed revised criteria of OLP and OLL as described in Chapter 4.

A study group of 173 patients, 62 patients diagnosed with OLP and 111 patients with OLL, according to revised, slightly modified WHO diagnostic criteria, was followed for periods ranging from 6.6 – 72.0 months, with a mean of 31.9 months. To explore the possibility of coincidental carcinomas, the expected number of patients with oral cancer in the group of OLP patients as well as in the group of OLL patients was estimated by applying the number of patients, age, sex, and length of follow-up to annual incidence rates of oral cancer for the general Dutch population. In evaluating whether the observed number of cases of cancer in the OLP group and the OLL group exceeded the expected number, the binomial test was employed.

Three out of 173 patients (1.7%), two men and one woman, developed a squamous cell carcinoma of the oral mucosa during follow-up. All malignant transformations occurred in the OLL group. The annual malignant transformation, based on a mean follow-up of 31.9 months, was calculated at 0.65 % per year. A comparison of the expected against actual figures for developing carcinomas showed no increase in OLP patients and a 219-fold increase in OLL patients, the latter being statistically not significant, but with a p-value of 0.083 suggesting at least a trend.

Our results give some support to the hypothesis that OLL are of a premalignant nature. Classical cases of OLP, clinically as well as histopathologically evident OLP, are probably innocuous. Before a final statement with regard to the premalignant character of OLP and OLL can be formulated, the present follow-up study should be prolonged and expanded with a larger number of patients. Until then, we advise to offer patients with OLP and OLL bi-annual follow-up examination. Follow-up will be particularly important in OLL patients with atrophic/erosive/ulcerative affections.

Introduction

Possible malignant transformation of OLP is the subject of an ongoing and controversial discussion in the literature. A case of carcinoma arising in lichen planus of the oral mucous membrane was first described by Hallopeau in 1910 (1). Ever since, several, mainly retrospective studies and case reports have been published on this subject (Table 1, Introduction) (2-21). The range of malignant transformation of OLP per year, as described in the literature, varies between 0.04 and 1.74%. Some authors have, therefore, accepted that OLP is of a premalignant nature. However, Krutchkoff and others have criticized this opinion (22). They reviewed the literature from the period 1950-1976 and accepted only 15 of 223 (7%) published cases as sufficiently documented by their criteria for malignant development of OLP. Their criticism was largely based on insufficient data to support the initial diagnosis of OLP, the lack of adequate historical data regarding prior exposure to carcinogens, and the occurrence of some of the oral cancers in an anatomic site remote from the OLP. Since Krutchkoff's report, a continuing number of follow-up studies and case reports have been published on the possible premalignant character of OLP. In 1999, we published a review of these reports and accepted only 33 out of 98 (34%) reported cases from the period 1977-1999 as sufficiently documented (Chapter 1)(23). Our literature review did not argue against the validity of some of the previous reported studies; rather, it underlined the need to be more specific when reporting this type of material. Therefore, we made a call for long-term prospective studies on this subject with detailed documentary data.

The present report describes the possible premalignant character of OLP and OLL of a prospectively followed cohort of patients with detailed documentary data applying the proposed revised diagnostic criteria of OLP and OLL as described in Chapter 4 (24).

Patients and methods

The prospective study included 343 patients, who had been initially referred to the Department of Oral and Maxillofacial Surgery of the Vrije Universiteit Medical Centre, Amsterdam, for diagnosis and management of OLP and OLL in the period February 1996 – February 2002. The group of 343 patients was restricted to those with a minimum follow-up

of six months; 249 patients fulfilled this criterion. A total of 21 patients refused biopsy and were thus excluded; from the remaining group of 228 patients there was no histologic support for OLP in 54 cases according to the applied revised, modified WHO diagnostic criteria of OLP and OLL (24), and one patient revealed to have squamous cell carcinoma at the initial biopsy (figure 5.1). According to the revised diagnostic criteria the remaining study group of 173 patients (113 females and 60 males) consisted of 62 patients with OLP and 111 patients with OLL (table 5.1). Patients' ages ranged from 23.1 to 79.2 years, with a mean of 52.2 years. The patients were followed for periods ranging from 6.6 – 72.0 months, with a mean of 31.9 months.

To explore the possibility of coincidental carcinomas, the expected number of patients with oral cancer in the present group of OLP patients as well as in the group of OLL patients was estimated by applying the number of patients, age, sex, and length of follow-up to annual incidence rates for the general Dutch population (7, 25). These tables give the average annual incidence rates per 100,000 by sex and five-year age groups. The estimates for each sex were calculated on the basis of the number of patients followed in each group multiplied by number of follow-up years and by average annual incidence rates for that group. Thereafter, estimates for each age group were summarized (Table 5.2 and 5.3). In evaluating whether the observed number of cases of cancer in the OLP group and the OLL group exceeded the expected number, the binomial test was employed.

Results.

Three out of 173 patients (1.7%), two men and one woman, developed a squamous cell carcinoma of the oral mucosa during follow-up. All malignant transformations occurred in the OLL group. The annual malignant transformation, based on a mean follow-up of 31.9 months, was calculated at 0.65 % per year. The length of follow-up before malignant development ranged from 11 – 70 months (mean: 33 months).

Characteristics of patients with malignant development are summarized in Table 5.4. Clinical photographs of all affected sites and biopsy specimen taken at the initial visit as well as clinical photographs and biopsy specimen of the tumor of each patient are shown in figure 5.2 – 5.4.

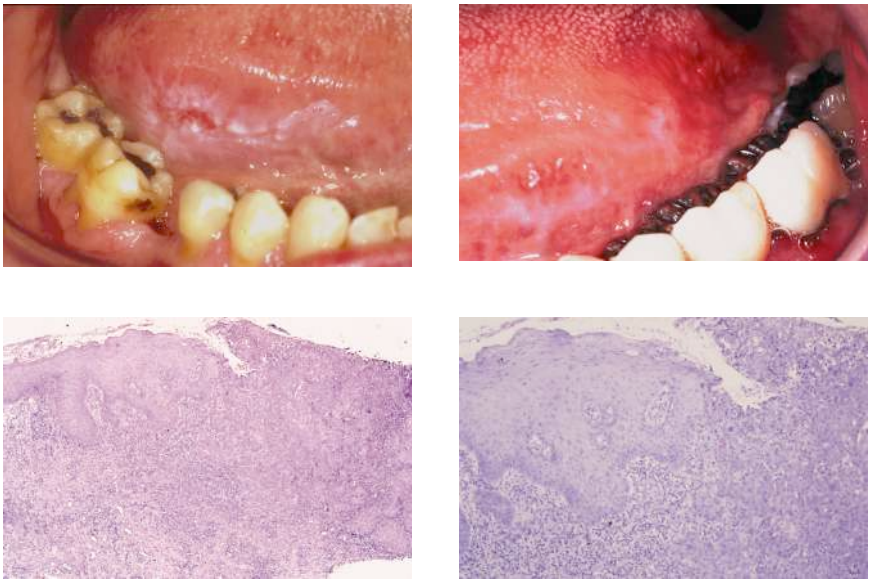


Figure 5.1. Patient with mucosal changes of both lateral borders of the tongue, clinically 'compatible with OLP'. An initial biopsy taken from the erosive lesion on the right lateral border of the tongue revealed to be a squamous cell carcinoma (haematoxylin-eosin, 5× and 10×); the patient was thus excluded from the follow-up study.

Table 5.1.
Final diagnosis of 173 study patients according to the proposed revised diagnostic criteria of OLP and OLL (24)

		histologic assessment		
		evident OLP	**compatible with OLP**	**total**
clinical assessment	**evident OLP**	62*	40	**102**
	compatible with OLP	38	33	**71**
	total	**100**	**73**	**173**

* 62 patients were finally diagnosed as OLP; the remaining 111 were diagnosed as OLL.

Table 5.2.
Calculation of estimated number of persons developing oral cancer during follow-up period in the OLP group (n=62)

AGE GROUP	NUMBER OF PATIENTS MULTIPLIED BY FOLLOW-UP YEARS FOR EACH AGE GROUP		AVERAGE ANNUAL INCIDENCE RATE PER 100,000 (25)		ESTIMATED NUMBER OF PERSONS WITH ORAL CANCER X 100,000	
	women	men	women	men	women	men
0-	0	0	0	0	0	0
5-	0	0	0	0	0	0
10-	0	0	0	0	0	0
15-	0	0	0	0	0	0
20-	0	2.25	0.6	0	0	0
25-	1.30	0	1.0	0	1.30	0
30-	5.42	1.61	1.6	0	8.67	0
35-	3.32	7.11	0	0	0	0
40-	14.17	7.67	2.2	1.6	31.17	12.27
45-	6.54	19.91	2.7	6.3	17.66	125.43
50-	5.81	19.93	0.8	8.7	4.65	173.39
55-	34.07	2.95	7.2	8.8	245.30	25.96
60-	17.62	9.64	3.7	12.8	65.19	123.39
65-	8.47	0	7.4	11.9	62.68	0
70-	4.62	0	9.6	20.2	44.35	0
75-	0	1.87	13.6	5.5	0	10.29
80-	0	0	5.1	15.0	0	0
85+	0	0	7.0	53.1	0	0
				Total	480.97	470.73
				Estimated number of persons	0.0048097	0.0047073

Table 5.3.
Calculation of estimated number of persons developing oral cancer during follow-up period in the OLL group (n=111)

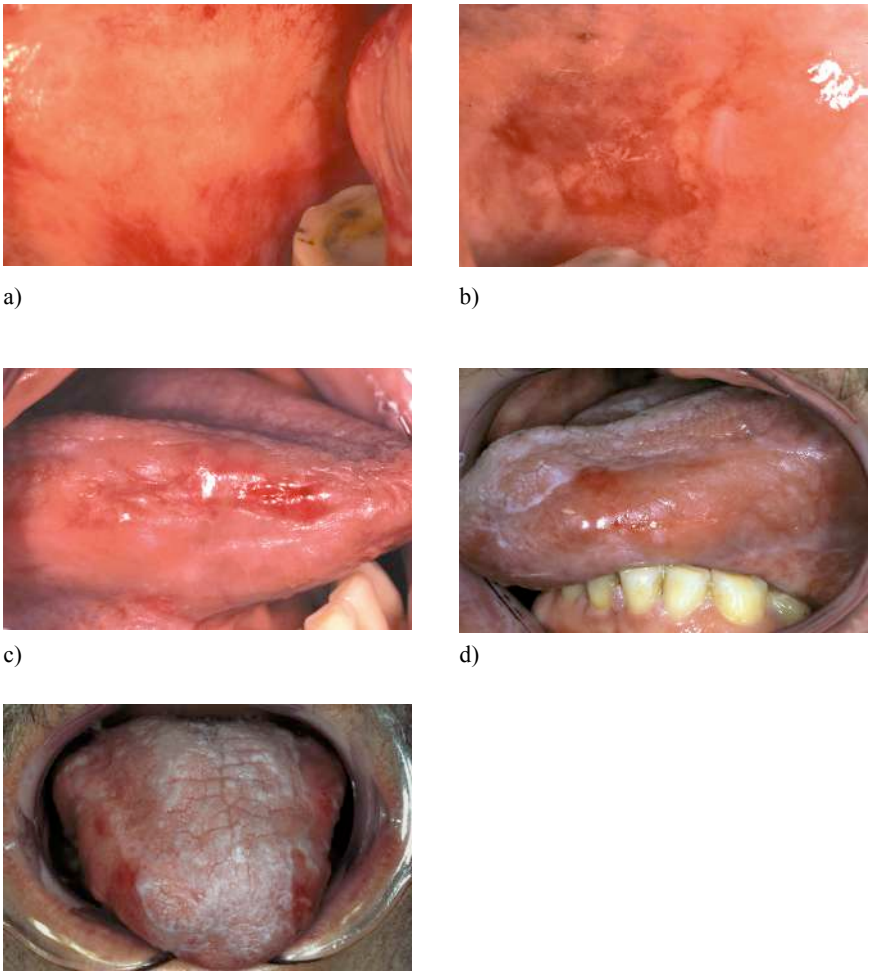
AGE GROUP	NUMBER OF PATIENTS MULTIPLIED BY FOLLOW-UP YEARS FOR EACH AGE GROUP		AVERAGE ANNUAL INCIDENCE RATE PER 100,000 (25)		ESTIMATED NUMBER OF PERSONS WITH ORAL CANCER X 100,000	
	women	men	women	men	women	men
0-	0	0	0	0	0	0
5-	0	0	0	0	0	0
10-	0	0	0	0	0	0
15-	0	0	0	0	0	0
20-	0	0	0.6	0	0	0
25-	3.03	0	1.0	0	3.03	0
30-	10.05	3.64	1.6	0	16.08	0
35-	19.48	6.35	0	0	0	0
40-	14.47	21.66	2.2	1.6	31.83	34.66
45-	9.98	20.48	2.7	6.3	26.95	129.02
50-	30.66	2.13	0.8	8.7	24.53	18.53
55-	53.86	18.81	7.2	8.8	387.79	165.53
60-	28.05	5.62	3.7	12.8	103.79	71.94
65-	15.39	3.25	7.4	11.9	113.89	38.68
70-	14.90	0	9.6	20.2	143.04	0
75-	4.28	0	13.6	5.5	58.21	0
80-	0	0	5.1	15.0	0	0
85+	0	0	7.0	53.1	0	0
				Total	909.14	458.36

Estimated number of persons	0.0090914	0.0045836

Table 5.4.
Characteristics of patients with malignant development during follow-up

	Sex	Age at malignant development	Site and stage of SCC	Cutaneous manifestations of OLP	Medical history	Internal drug therapy	Topical drug therapy at site of SCC	Tobacco usage	Daily alcohol consumption	Died of disease
1	M	42	Left lateral border of tongue (T1N0M0)	Yes	Ulcerative colitis Hashimoto's disease Nephrotic syndrome Pancreatitis Haemolytic anaemia	Prednisone Thyroxine Omeprazole	Fluocinonide for several years before development SCC	None	None	Yes
2	F	76	Right lateral border and base of tongue (T4N2bM0)	No	-	None	Fluocinonide and dexamethasone for several months before development SCC	None	None	Yes
3	M	64	Right lateral border of tongue (T1N0M0)	No	-	None	Fluocinonide for several years before development SCC	None	None	No

SCC = squamous cell carcinoma

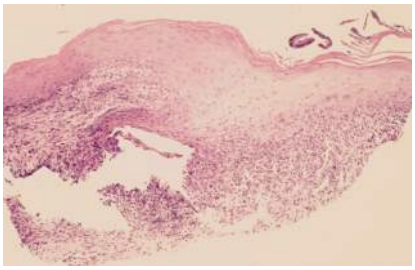


a) b)

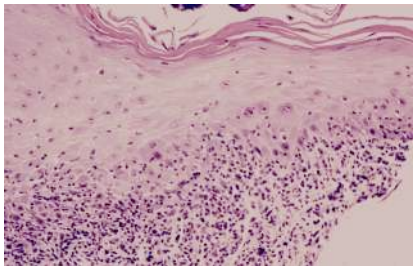
c) d)

e)

Figure 5.2. Clinical pictures of patient 1 (see Table 5.4) taken at first visit showing extensive atrophic/erosive changes of the buccal mucosa (a+b), mixed reticular/atrophic/erosive changes of the lateral borders of the tongue (c+d), as well as plaque-type changes of the dorsum of the tongue (e), clinically being 'compatible with OLP'.

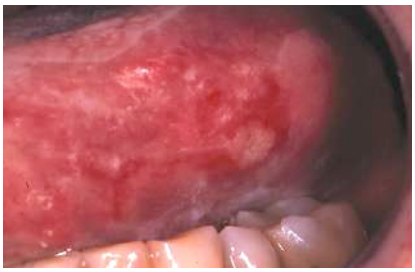


f)

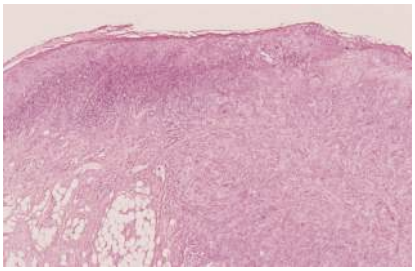


g)

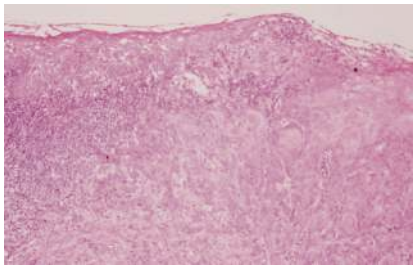
Figure 5.2. A biopsy specimen from the left lateral border of the tongue from patient 1 showed also characteristics being 'compatible with OLP' (haematoxylin-eosin, 10× (f), and 20× (g)).



h)

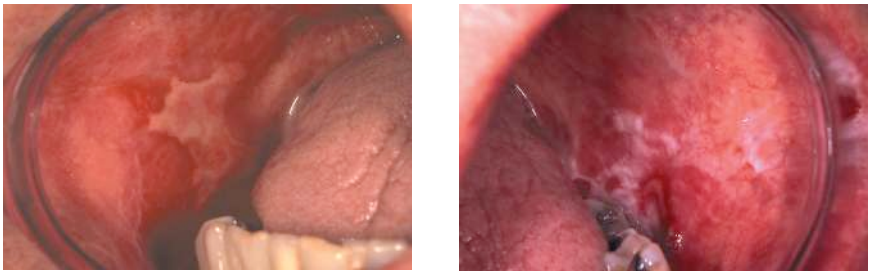


i)

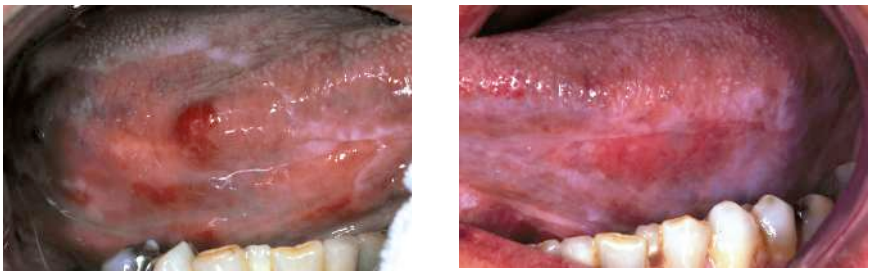


j)

Figure 5.2. An indurated lesion arising from the erosive lesion on the left lateral border of the tongue 19 months after first visit (h) (patient 1). Histopathological examination showed a moderate – well differentiated squamous cell carcinoma (haematoxylin-eosin, 5× (i), and 10× (j)).

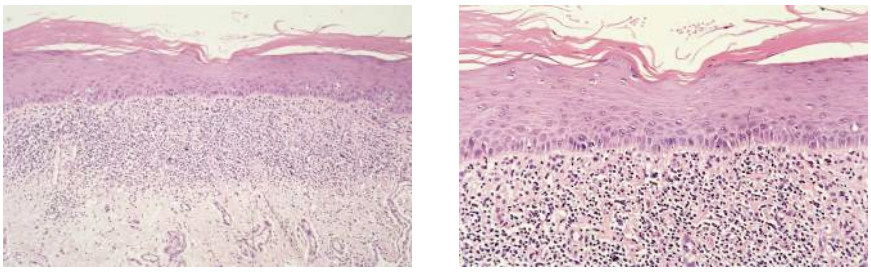


a) b)



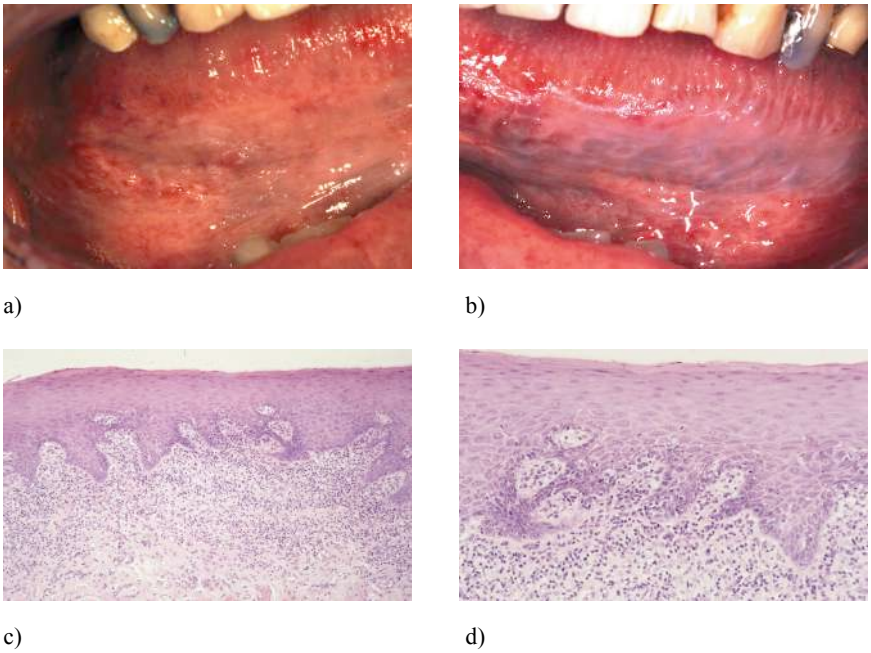
c) d)

Figure 5.3. Clinical pictures of patient 2 (see Table 5.4) taken at first visit showing extensive mixed atrophic/erosive and reticular changes of the buccal mucosa (a+b), and the lateral borders of the tongue (c+d), clinically being 'compatible with OLP'.



e) f)

Figure 5.3. A biopsy specimen from the right lateral border of the tongue from patient 2 showed also features 'compatible with OLP' (haematoxylin-eosin, 10× (e), and 20× (f)).

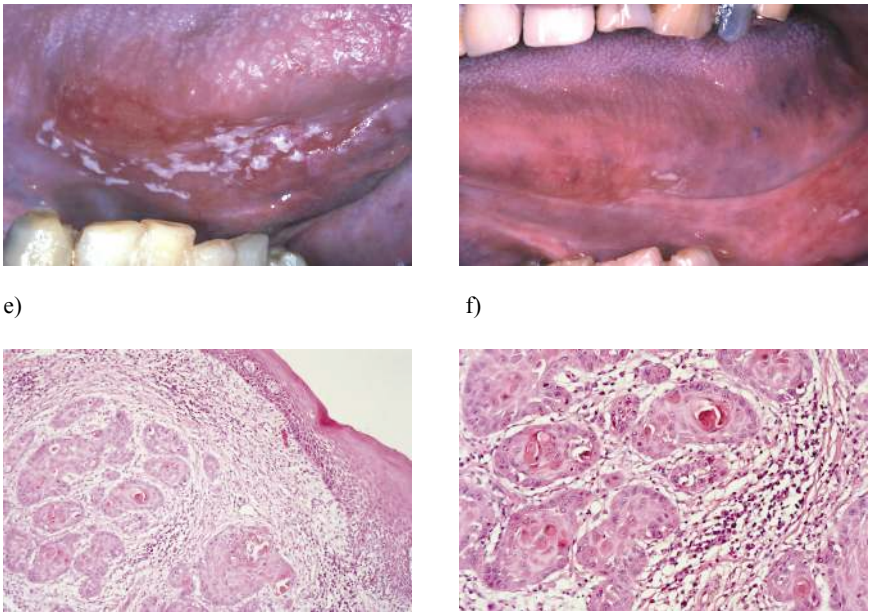


a) b)

c) d)

Figure 5.4. Clinical pictures of patient 3 (see Table 5.4) taken at first visit showing mild reticular changes of the lateral borders of the tongue, on the left side more prominent than on the right (a+b), clinically being 'compatible with OLP'. A biopsy specimen showed a diffuse lymphocytic infiltrate with some changes of basal cell degeneration, histologically being 'compatible with OLP' (haematoxylin-eosin, 10× (c), and 20× (d)).

The corresponding figure for oral cancer in a similar group from the general population was 0.0095 in the OLP group (Table 5.2) and 0.0137 in the OLL group (Table 5.3). A comparison of the expected against actual figures for developing carcinomas showed no increase in OLP patients and a 219-fold (3/0.0137) increase in OLL patients. The latter being statistically not significant, but with a p-value of 0.083 suggesting at least a trend.



e) f)

g) h)

Figure 5.4. An erosive lesion on the right lateral border of the tongue surrounded by whitish changes that could be scraped off, compatible with pseudomembranous candidiasis, 70 months after first visit (patient 3). On palpation some induration was noticed (a). On the left lateral border of the tongue previously present reticular affections were changed into a mild erosive lesion (b). Histopathological examination showed a moderate – well differentiated squamous cell carcinoma (haematoxylin-eosin, 10× (g), and 20× (h)).

Discussion.

As the main criticism on studies publishing on the possible premalignant character of OLP consists of lack of sufficient data to support the initial diagnosis of OLP in cases that finally developed a squamous cell carcinoma (22,23), we applied, revised, modified WHO diagnostic criteria of OLP and OLL (24). Using these strict criteria 24% (55/228) of the patients initially referred to our clinic were excluded as the diagnosis could not be supported by histology, 49% (111/228) were categorized as OLL, and in only 27% (62/228) a final diagnosis of OLP could be established. The relatively low percentage of the latter might also be caused by the possible selective nature of the study group due to referral

bias. Clinical and histopathological 'classical' cases of OLP are probably less likely to be referred.

All three malignant transformations occurred in the OLL group. An increased change of malignant transformation of 219-fold was calculated for this specific group. Although statistically not significant, due to the small size of population and the short duration of follow-up, there seemed to be at least a trend. Holmstrup et al. found a significant 50-fold increase in OLP patients in a similar study and comparable calculation (7). As they applied different inclusion criteria part of their OLP group consisted probably also of patients with OLL.

In accordance with several authors who reported that malignant transformations are more likely to occur in atrophic, erosive and ulcerative lesions, all the malignancies in the present study developed in erosive lesions. It has been stated that the atrophic, erosive and ulcerative forms predispose the mucosa to damage from carcinogenic agents. However, none of our patients were smokers nor drank alcohol on a daily basis, suggesting that carcinomatous development is part of the natural evolution of OLL or is due to presently unknown extrinsic factors other than alcohol and tobacco. In our third patient developing a malignancy such a factor might has been a Candida albicans infection. It has been hypothesized that strains of Candida albicans are able to catalyze the formation of the carcinogen N-nitrosobenzylmethylamine (26).

Immunemodulating agents such as topical and systemic corticosteroids are commonly used to reduce inflammation and restore comfort in cases of OLP and OLL. There is still debate whether the application of such agents is contraindicated in OLP and OLL since this therapy could depress local cell-mediated immunity and thus, may promote the progression of malignant development (27). It has been stated that corticosteroid therapy could not only hasten the development of a malignancy, but that it would do so with reduced symptoms. This would thus increase the chance of progression to an advanced state before the condition is ultimately diagnosed and treated. All our patients used topical corticosteroids at the site of malignant transformation for extended periods. One patient did even use, periodically, systemic corticosteroids because of an ulcerative colitis. Whether those therapies have, indeed, played a role in malignant transformation remains a matter of debate.

In summary, our experience gives support to the hypothesis that OLL are of a premalignant nature. Classical cases of OLP, based on both clinical and histopathological criteria are probably innocuous. Before a

final statement with regard to the premalignant character of OLP and OLL can be formulated the present follow-up study should be prolonged and expanded with a larger number of patients. Until then, we advise to offer patients with OLP and OLL bi-annual follow-up examination. Follow-up will be particularly important in OLL patients with atrophic/erosive/ulcerative affections.

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CHAPTER 6

COST-EFFECTIVENESS ANALYSIS OF SCREENING FOR THE POSSIBLE DEVELOPMENT OF CANCER IN PATIENTS WITH ORAL LICHEN PLANUS

E.H. van der Meij[1]
P.D. Bezemer[2]
I. van der Waal[1]

1 Department of Oral and Maxillofacial Surgery/Oral Pathology, Academic Centre for Dentistry Amsterdam (ACTA)/Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

2 Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Vrije Universiteit, Amsterdam, The Netherlands

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Abstract

Several authors have expressed the view that patients with OLP are at increased risk of developing oral cancer. Since OLP cannot be effectively treated, regular screening for the possible development of oral cancer might be considered.

The purpose of the present study was 1) to calculate costs and effectiveness of screening for oral cancer in OLP patients with a decision model, 2) to compare the cost-effectiveness of different screening scenarios, and 3) to perform a sensitivity analysis of several variables used in this model.

Costs and effectiveness of a population of 100,000 OLP patients, being either screened or not screened for oral cancer, were calculated for the period of 1 year. Health gain was expressed as quality adjusted live years (QALY's) and equivalent lives saved (ELS). Cost-effectiveness was expressed as extra costs (costs of screening minus costs of no screening) per ELS. Then, the outcome was compared with the cost-effectiveness of a different screening scenario. Finally, the effect of varying the variables 1) costs of cancer treatment, 2) annual malignant transformation rate (MTR), 3) sensitivity and specificity of an oral examination, and 4) proportion of cancers found in stage I on extra costs per ELS were assessed in a sensitivity analysis.

The health gain from screening was 592 QALY's or the equivalent of 23.68 lives saved costing 1,265,229 dollar, meaning that one ELS costed 53,430 dollar. Increase of cancer treatment costs will significantly decrease the costs per ELS. When the MTR is lower than 0.4% per year, extra costs per ELS will increase exponentially. The effect of sensitivity and specificity of an oral examination in detecting oral cancer on cost-effectiveness seems to be substantial. When the proportion of cancers found in stage I can be increased from 40% (without screening) up to at least 60% after screening, extra costs per ELS will decrease exponentially.

Screening for oral cancer in OLP patients, based on the presently used model, seems attractive. However, varying the several variables in the decision model has a significant impact on the final costs and effectiveness. Only, when additional information about these variables will become available, a more precise and realistic calculation can be performed.

Introduction

There are about 600 newly diagnosed cases of oral cancer in the Netherlands each year, i.e., an overall incidence of about 4 per 100,000 per annum representing between 1 and 2% of the total number of malignancies (1,2). Oral cancer treatment is associated with significant physical and psychological morbidity while mortality remains high with approximately 50% of patients dying of their disease within 5 years (2). Survival is largely related to the size of the primary tumour at first presentation (3). Therefore, promoting early detection of oral cancer through prevention strategies such as screening, particularly of population groups at risk, such as heavy smokers and drinkers, seems to be important in reducing the morbidity and mortality from oral cancer (4). In order to evaluate the benefits from such a screening programme Downer et al. developed a decision model to simulate the process of population screening for oral cancer (5,6).

Several authors have expressed the view that patients with OLP are also at risk of developing an oral malignancy, the malignant transformation rate (MTR) varying from 0.04 to 1.74% (Table 1, Introduction) (7-23). Regular screening of patients affected with OLP in order to detect the possible development of oral cancer in an early stage might thus reduce morbidity and mortality from oral cancer. However, no evidence of the cost-effectiveness of such an approach is available.

The objectives of the present study were 1) to calculate costs and effectiveness of screening for oral cancer in OLP patients using the decision model as has been described by Downer et al. (5), 2) to compare the cost-effectiveness of different screening scenarios, and 3) to perform a sensitivity analysis assessing the effect of varying several variables used in this model on the cost-effectiveness.

Methods

Part 1. Calculation of costs and effectiveness of screening for oral cancer in OLP patients in the Netherlands

Calculation of costs and effectiveness was performed by applying the decision model as has been previously described by Downer et al. (5). Assumptions and abbreviations used in the model are summarized in table 6.1.

The analysis was performed in a hypothetical population of 10,000,000 people, which is the population of the Netherlands over the age of 15 years. The prevalence of OLP was set at 1% (24). OLP patients were assumed to be aged on average 55 years (25). The annual malignant transformation rate of OLP was set at 0.2%, which approaches the median of the reviewed studies in Table 1 of the Introduction (median = 0.26). Thus, cost and effectiveness of a population of 100,000 OLP patients, being either screened or not screened for oral cancer, were calculated for a period of 1 year.

1.1 No screening (figure 6.1)

Among the 200 OLP patients who developed oral cancer in 1 year, the proportion of cancers found in stage I and stage II+III+IV (stage II+) was estimated to be 40% and 60%, respectively (26).

1.1.1 Costs

In the absence of solid figures of the costs of oral cancer treatment in the Netherlands, the costs of treatment of stage I and stage II+ were estimated at 3,000 and 23,000 dollar per case, respectively. These costs represented only direct medical costs.

1.1.2 Effectiveness

Health gain was expressed as quality adjusted live years (QALY's) (27) and equivalent lives saved (ELS). The concepts of cancer and quality points as described by Eddy (28) were incorporated in the model in terms of Von Neumann and Morgenstern utilities (29).

Health state utilities for oral cancer assessed by Downer et al. were used, being 0.88 for stage I cancer and 0.68 for stage II+ cancer (4). The health state utility of OLP, deduced from the overall health state utility of oral precancer was set at 0.92 (4).

Life expectancy was calculated from the 5-year survival rates for oral cancer, assuming that a healthy 55-year old individual in the Netherlands has a 25-year life expectancy (30). Thus, patients with stage I cancer were supposed to have a life expectancy of 18.75 years (75% of cases surviving 25 years) (31) and stage II+ an expectancy of 8.325 years

Table 6.1.
Abbreviations of variables used in the model, including values of scenario A, B and C

VARIABLE	ABBREVIATION	SCENARIO A	SCENARIO B	SCENARIO C
Hypothetical population	POP	10,000,000	10,000,000	10,000,000
Prevalence of OLP[24]	PREV	0.01	0.01	0.01
Malignant transformation rate of OLP (per year)[7-23]	MTR	0.002	0.002	0.002
Frequency of screening (per year)	FREQ	-	1	1
Attendance screening	AT	-	0.50	0.75
Life expectancy of healthy 55-year old individual[30]	LE	25	25	25
5-years survival oral cancer (all stages)[31]	SUR (AS)	0.50	0.50	0.50
5-years survival oral cancer (stage I)[31]	SUR (SI)	0.75	0.75	0.75
Percentage oral cancer stage I of all stages[26]	%SI	0.40	1	1
Health state utility OLP patients	HSU (OLP)	0.92	0.92	0.92
Health state utility oral cancer stage I[4]	HSU (SI)	0.88	0.88	0.88
Health state utility oral cancer stage II+[4]	HSU (SII+)	0.68	0.68	0.68
Sensitivity oral exam for screening oral cancer[32]	SENS	-	0.91	0.80
Specificity oral exam for screening oral cancer[32]	SPEC	-	0.92	0.80
Costs screening (in dollars)	COSTS SCREEN	-	42	12
Costs biopsy by specialist (in dollars)	COSTS BIOPSY	-	63	105
Costs oral cancer treatment per case (all stages, in dollars)	COSTS TREAT (AS)	15,000	15,000	15,000
Costs oral cancer treatment per case (stage I, in dollars)	COSTS TREAT (SI)	3,000	3,000	3,000
Costs oral cancer traetment per case (stage II+, in dollars)	COSTS TREAT (SII+)	23,000	23,000	23,000

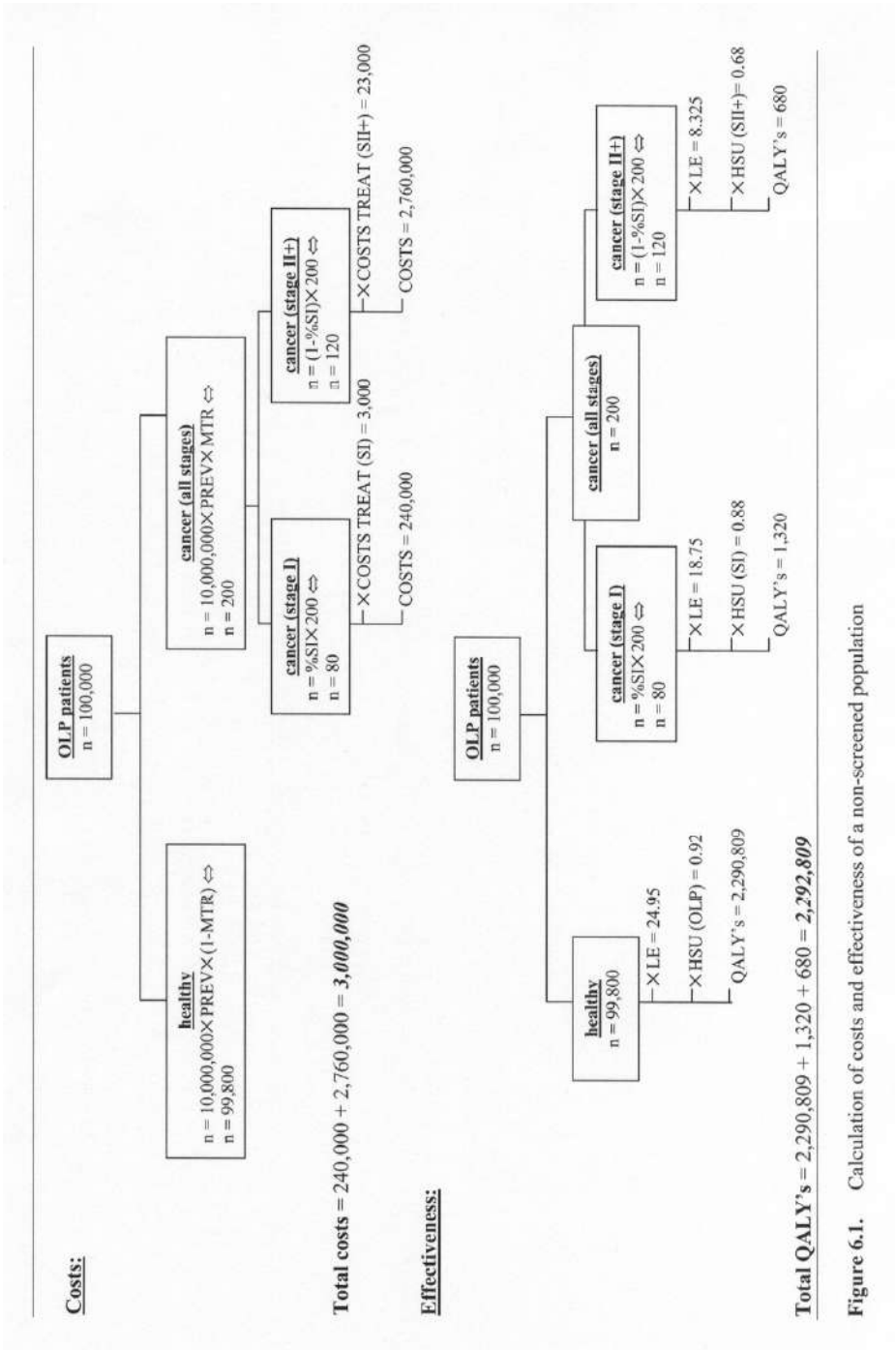

Figure 6.1. Calculation of costs and effectiveness of a non-screened population

(33.3% of cases surviving 5 years) (31). For OLP, the malignant transformation rate was set at 0.2%, meaning that 99.8% of OLP patients would survive 25 years, resulting in an overall life expectancy of 24.95 years. These calculations were based on the assumption that the outcome of having any oral cancer was either immediate death or 25 year survival. According to Downer et al.'s model (5), this assumption was made for the practical purpose of arriving at an average life expectancy for cancer at each stage.

1.2 Screening (figure 6.2 and 6.3)

A figure of 50% of initial attendance of the screening program was adopted. Costs and effectiveness of patients not responding to the screening program were calculated as described in the 'no screening' section (1.1). Frequency of screening was set at once a year.

Validity of the screening examination in detecting oral cancer, which would consist of clinical examination of the oral mucosa, was expressed in terms of sensitivity and specificity. Screening would be carried out by oral specialists (oral and maxillofacial surgeons) with a sensitivity of 0.91 and a specificity of 0.92 (32). Given these figures, there were 4,083 subjects testing positive (91 true positive (TP), 3,992 false positive (FP)) and 45,917 subjects testing negative (45,908 true negative (TN), 9 false negative (FN)). Screening was supposed to help to detect the oral cancer in an early stage (stage I). Screened false negative subjects were assumed to have stage I cancers in 40% and stage II+ cancers in 60% of cases (26).

1.2.1 Costs

Screening by a specialist in the Netherlands would cost 42 dollar per visit. Subjects testing positive at examination would require an incisional biopsy, costing 63 dollar. In case of detecting a malignancy (stage I), costs of treatment were estimated at 3,000 dollar per case. Costs of cancer treatment of false negative subjects were calculated as described in 1.1.1.

1.2.2 Effectiveness

Effectiveness of screening was expressed as QALY's and ELS and calculated as described previously (1.1.2).

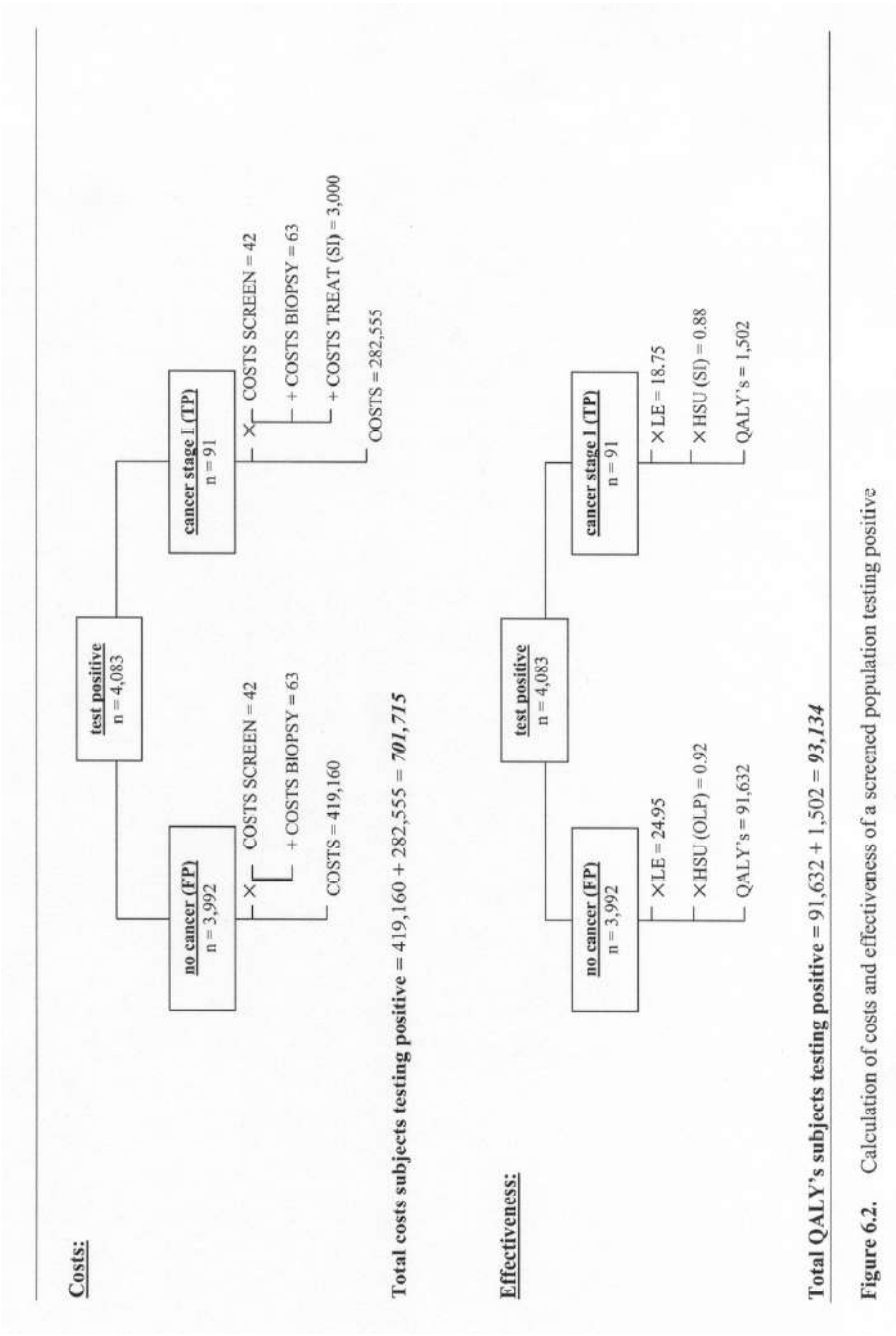

Figure 6.2. Calculation of costs and effectiveness of a screened population testing positive

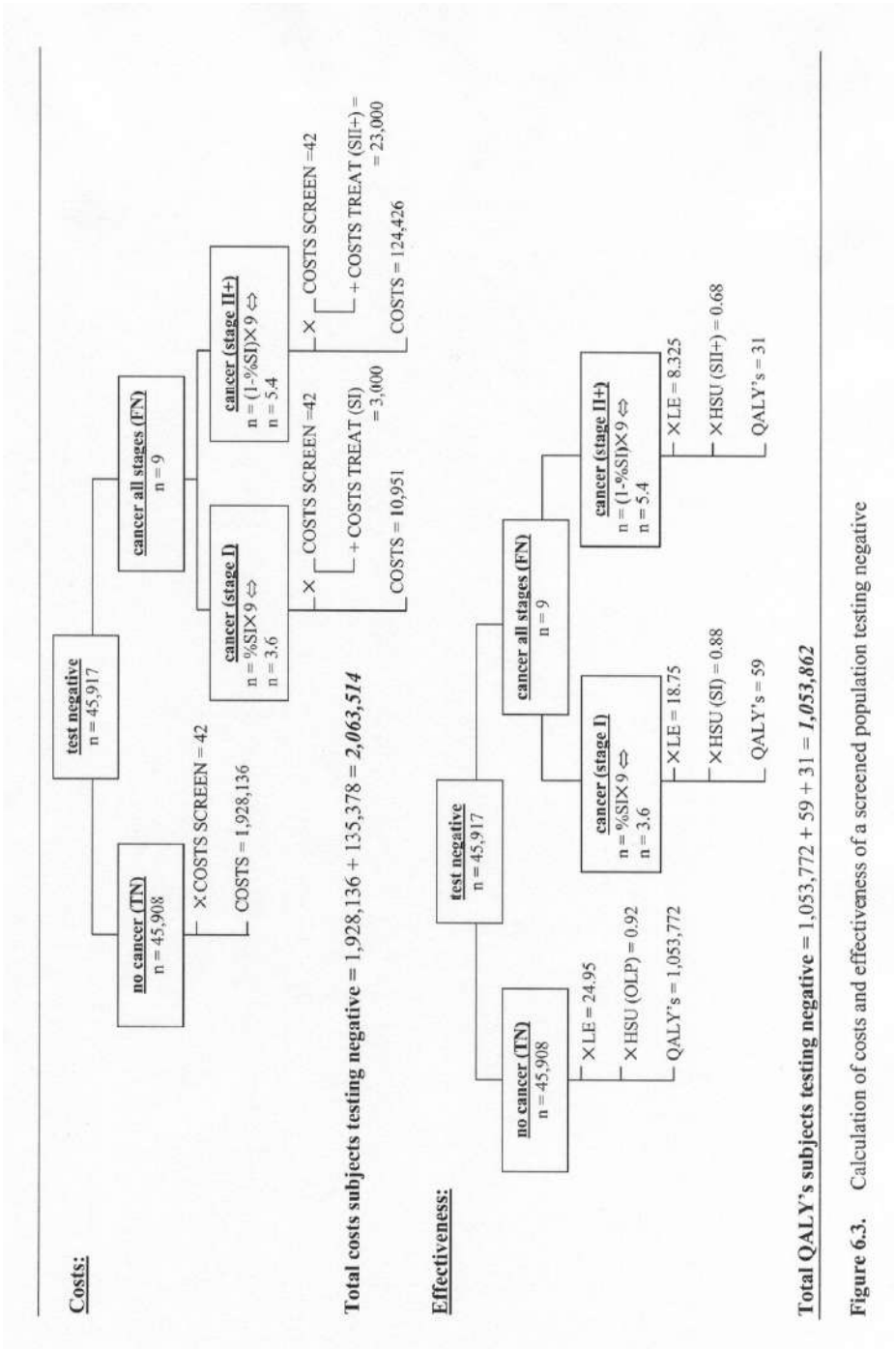

Figure 6.3. Calculation of costs and effectiveness of a screened population testing negative

Part 2. Comparison of the cost-effectiveness of different screening scenarios

The no screening decision model presented in paragraph 1.1 was called scenario A. Costs and effectiveness of two different screening scenarios (scenario B and C) were compared with scenario A.

Scenario B. Screening will be performed by specialists as presented in paragraph 1.2.

Scenario C. Screening will be performed by dentists with reduced validity of the screening examination in detecting oral malignancies (SENS = 0.8, SPEC = 0.8) (32), and with decreased screening costs (COSTS SCREEN = 12). In case of a positive test the patient would be referred to a dental specialist for taking a biopsy, costing 42+63=105 dollar. Response to the screening programme was increased from 50 to 75%.

Part 3. Sensitivity analysis

The effects of varying the variables 1) costs of cancer treatment, 2) MTR, 3) sensitivity and specificity of an oral examination, and 4) proportion of cancers found in stage I on extra costs (costs of screening minus costs of no screening) per ELS were assessed. Calculations were performed using scenario B as baseline scenario.

Results

Part 1. Figure 6.1 shows the costs accruing to those who were not screened, being 3,000,000 dollar. Total costs of screening, as shown in figure 6.2 and 6.3, were costs of subjects screened and categorized as positive or negative added to the costs of those not attending screening (701,715 + 2,063,514 + (0.5✕3,000,000) = 4,265,229 dollar). Extra costs of screening compared with no screening were thus 4,265,229 – 3,000,000 = 1,265,229 dollar.

The overall QALY's in the non-screened population amounted to 2,292,809 (figure 6.1). Total QALY's of the screened population, summed at the foot of figures 6.2 and 6.3, added to the QALY's of the population not responding to the screening were 93,134 + 1,053,862 + (0.5✕2,292,809) = 2,293,401. It follows that the health gain from screening was 2,293,401 – 2,292,809 = 592 QALY's or the equivalent of

592/25 = 23.68 lives saved, meaning that one ELS costed 1,265,229/23.68 = 53,430 dollar.

Part 2. Extra costs due to screening and QALY's saved of each scenario are shown in figure 6.4.

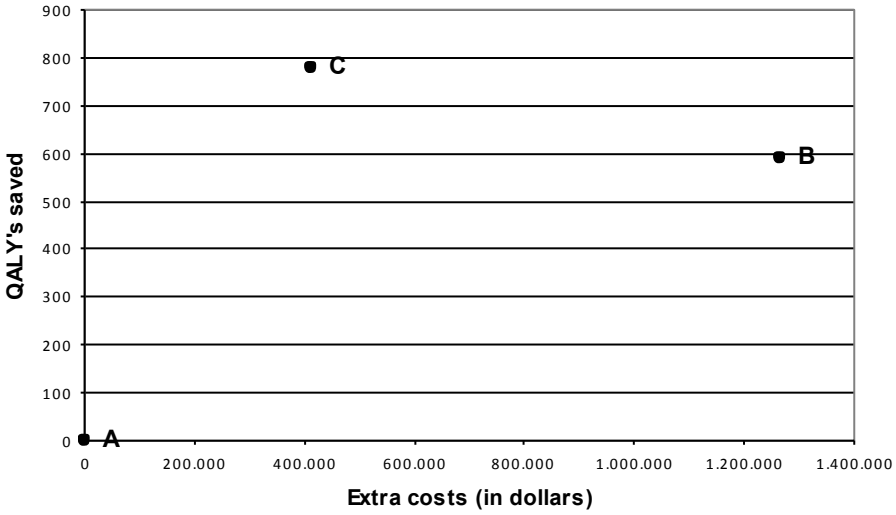

Figure 6.4. Effectiveness and costs of scenario A, B, and C

Part 3. The effects of varying the variables 1) costs of cancer treatment, 2) MTR, and 3) sensitivity and specificity of an oral examination, and 4) proportion of cancers found in stage I on extra costs per ELS are shown in figures 6.5, 6.6, 6.7 and 6.8, respectively.

Discussion

Carrying out an assessment of the possible costs and effectiveness of screening for the development of cancer in patients affected with OLP is clearly a complex exercise involving many parameters. Since many poorly defined variables are involved, the result will at best be a crude approximation to real life. Nevertheless, the estimates are likely to be better than could be arrived at by intuition only (5).

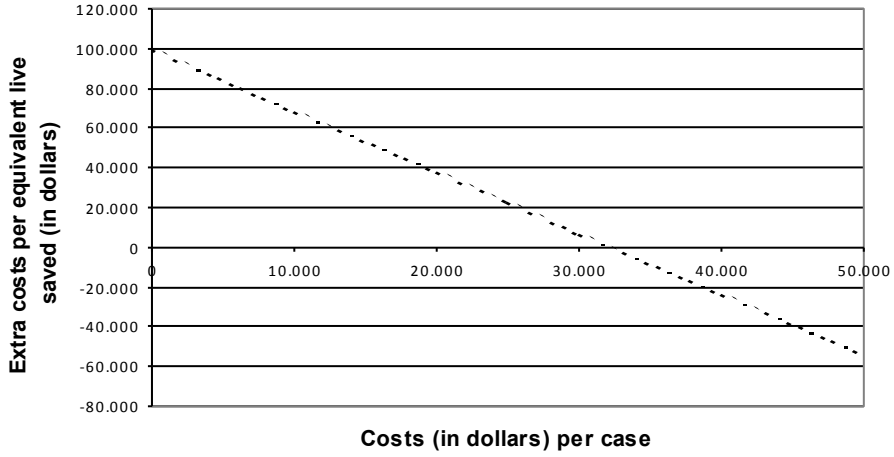

Figure 6.5. Effect of cancer treatment costs on extra costs per equivalent live saved

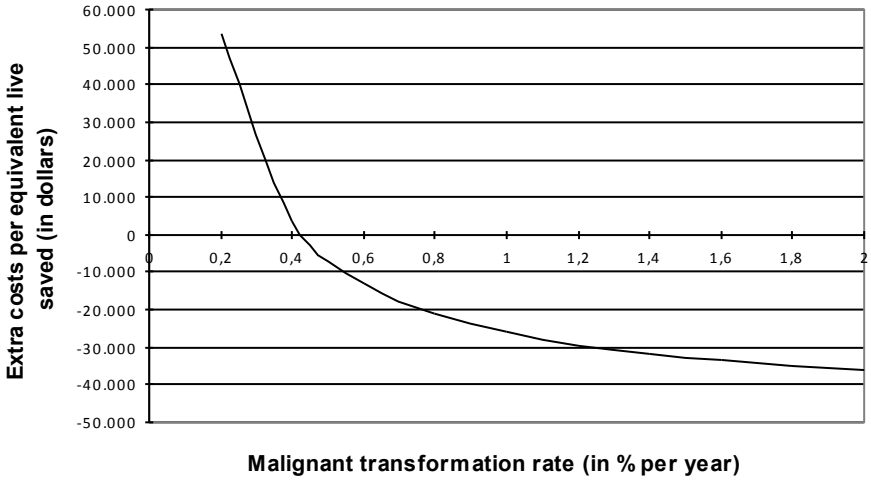

Figure 6.6. Effect of malignant transformation rate on extra costs per equivalent live saved

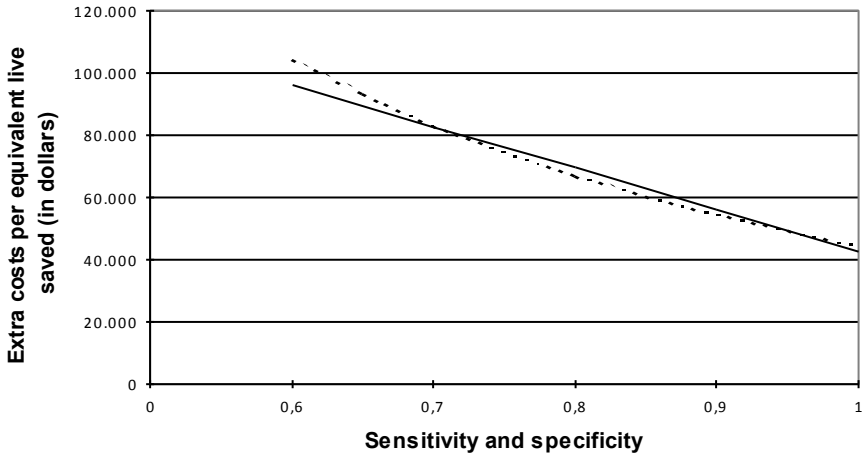

Figure 6.7. Effect of sensitivity and specificity on extra costs per equivalent live saved (---- = sensitivity, ——= specificity)

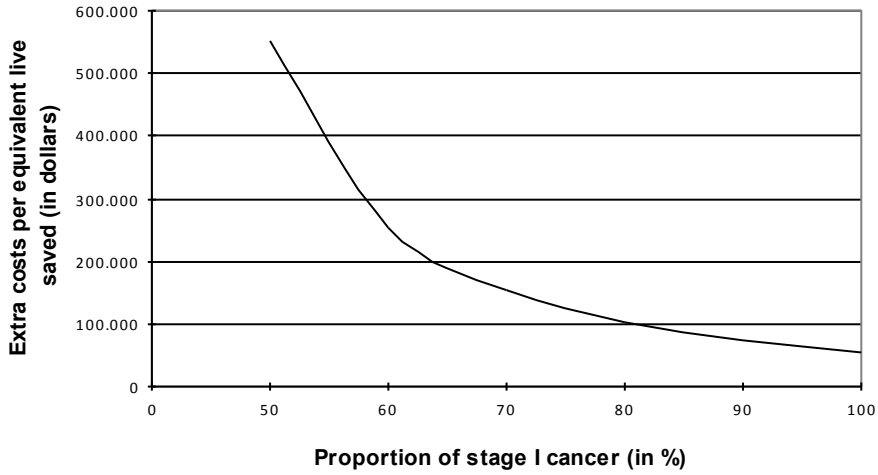

Figure 6.8. Effect of proportion of stage I cancers on extra costs per equivalent live saved

Based on the presently used decision model it was calculated that screening a hypothetical population of patients with OLP for the development of oral cancer would save the equivalent of 23.68 deaths per year per 100,000 subjects examined. The marginal cost-effectiveness was calculated as 53,430 dollar per life saved. Whether this can be considered expensive or cheap depends on the economic position of the country involved and the value that country places on a human life. Of the latter, no such figure is available for the Netherlands. In Japan, for example, a country with high costs of medical care, the value of a life was calculated as the equivalent of 200,000 – 300,000 dollar (39). In the Netherlands, costs of medical care are also at a high level; 53,430 dollar per life saved will probably be cheap enough to make screening attractive in this particular situation. Screening in countries with high medical costs is probably more attractive than in countries where these costs are relatively low (figure 6.5). From figure 6.5 one can conclude that increase of costs of cancer treatment will decrease the costs per ELS.

From figure 6.6 it can be concluded that when the MTR is lower than 0.4% per year, extra costs per ELS increase exponentially, making screening less attractive. In a review of the recent literature regarding malignant transformation of OLP, as described in Chapter 1, it was argued that the MTR is likely to be much lower than the average figure of 0.2% (40). It was stated that higher malignant transformation rates, as being reported in some studies, might be due to 1) the occurrence of malignant transformations that were in fact not cases of OLP and/or 2) the highly selected populations (i.e., the types of subjects most often referred for evaluation and treatment) used in those studies. When this statement is true, screening for oral cancer in OLP patients seems not to be cost-effective.

In the present calculation the prevalence of OLP was assumed to be 1%. In epidemiological studies on oral white lesions a wide range of prevalence rates of OLP were found, varying from 0.02 to 1.89% (13, 33-38, 41-50). These variations are likely to be caused by the study design and patient characteristics used in those studies. The prevalence rate of OLP has a major impact on the costs of screening as well as on the final yield of QALY's. A prevalence rate of 0.1% will largely decrease the screening costs as well as the total number of QALY's. Compared with the baseline scenario extra costs per ELS will remain unchanged. From this perspective, the prevalence rate of OLP seems not to influence the attractiveness of screening.

In the baseline scenario screening was performed by dental specialists, i.c., oral surgeons. As one can conclude from figure 6.4 screening by dentists will give a significant decrease in screening costs. Sensitivity and specificity of an oral examination in detecting oral cancer are lower when performed by dentists (32). Attempts to increase sensitivity and specificity by offering dentists specific training programmes in the detection of malignant lesions and the introduction of additional diagnostic tools such as vital staining with toluidine blue and/or exfoliative cytology have been advocated by several authors (51-53). From figure 6.7 it can be concluded that the effect of increasing sensitivity and specificity on cost-effectiveness in terms of costs per ELS is substantial. However, attempts to increase these parameters are involved with extra costs at the same time, e.g. costs of training programmes. These costs have not been included in the present calculation.

In several studies a low compliance rate was found for invitational screening programmes (54,55). In order to achieve a higher rate of attendance opportunistic screening, i.c., oral screening by the family dentist as part of routine dental check-ups, seems to be more appropriate. Although increased attendance of a screening programme will increase screening costs, it equally will increase the number of QALY's. From figure 6.4 it can be concluded that the gains from the higher attendance rate of 75% and lower screening costs associated with dental screening offset the losses from lower sensitivity and specificity in scenario C (compared with B).

In scenario B we assumed that if a screening programme was implemented, no one represented with stage II+ cancer. Downer et al. assumed in their analysis that implementation of a screening programme would reduce the proportion presenting with stage II+ from 60% with no program to 40% with the programme (5,6). However, no data exist supporting these assumptions. The effect of the proportion of cancers found in stage I on extra costs per ELS were therefore assessed in a sensitivity analysis. From figure 6.8 it can be concluded that when the proportion of cancers found in stage I can be increased from 40% (without screening) up to at least 60% after screening extra costs per ELS will decrease exponentially. Screening might thus be attractive when a screening programme enables us to detect at least 60% of the oral cancers in an early stage.

Screening inevitably carries a psychological burden, particularly in case of false positive or false negative results. Some of those who are

screened positive and referred for biopsy will subsequently be found not to have an oral malignancy (false positives). It might be expected that this would be a source of relief, but this assumption is not supported by the few studies that have followed up such patients in other screening programmes. Once the seeds of doubt have been sown they seem to be difficult to remove (56). Possibly, if the risk of a false positive result is fully explained by the referral for biopsy such adverse effects might be diminished. Also a negative result given without explanation or advice may have unwanted effects. It may bolster a pre-existing sense of invulnerability, and make patients less likely to return for subsequent visits or may lead to an increased patient delay in case of signs and symptoms of oral cancer. To date, there have been no studies to assess how people interpret a negative result or how it affects their subsequent behaviour. Some authors have gone so far as to call for a halt to screening until such data are available (57).

The present study has provided only provisional estimates of the possible costs and effectiveness of screening for the possible development of cancer in patients affected with OLP. Since varying the several variables in the decision model seems to have a significant impact on the final calculated costs and effectiveness, further research of these variables, especially of their combined effect, is needed. Variables that will need further study are the costs involved in oral cancer treatment, the MTR of OLP, the prevalence of OLP, the effect of screening on detection of early-stage cancer, as well as the psychological burden and benefits of screening. Only, when additional information about these variables will become available, a more precise and realistic calculation can be performed.

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SUMMARY

Possible malignant transformation of oral lichen planus (OLP) is the subject of an ongoing and controversial discussion in the literature. The range of malignant transformation of OLP per year, based on mainly retrospective follow-up studies, varies between 0.04 and 1.74%. Some authors have, therefore, accepted that OLP is regarded to be a premalignant condition, being defined as 'a generalized state associated with a significant increased risk of cancer'. The major problem in this discussion are the inclusion criteria that are used in the aforementioned follow-up studies. Since there are no universally accepted diagnostic criteria for OLP, the diagnostic approaches of the studies vary. Besides, it is well recognized that both clinical and histopathological criteria of OLP, such as proposed by the World Health Organization (WHO) in 1978, leave room for subjectivity in the interpretation. In this thesis the possible premalignant character of OLP and oral lichenoid lesions (OLL) has been investigated from a clinicopathological perspective.

In **chapter 1** a critical review of the clinicopathological literature on the possible premalignant character of OLP from the period 1977-1999 has been described. Based on a literature review from the period 1950-1976, Krutchkoff et al. questioned the possible premalignant nature of OLP. Their criticism was largely based on insufficient data to support the initial diagnosis of OLP. In the present review, using the same criteria as being used by Krutchkoff et al., thirty-three out of 98 (34%) reported cases were accepted as sufficiently documented evidence of malignant transformation of OLP. Although this percentage was somewhat higher than the percentage reported by Krutchkoff et al., it was concluded that there is a need for uniformly accepted criteria to establish a firm diagnosis of OLP. It was stated that, only when such criteria are available, long-term prospective studies on the suggested possible premalignant nature of OLP are feasible.

In **chapter 2 and 3** the validity of the clinical and histopathological definition of OLP, as proposed by the WHO in 1978, was studied evaluating interobserver and intraobserver variability in the clinical and histopathological assessment of OLP. Interobserver and intraobserver variability were assessed by calculation of unweighted kappa statistics. It was demonstrated that interobserver agreement in the clinical and histologic assessment of OLP defined by kappa varied from moderate to substantial, and from poor to moderate, respectively. Intraobserver agreement appeared to be significantly better in both studies. The results

of this study indicate that diagnostic assessment of OLP, based on the available WHO definition, is a rather subjective and insufficiently reproducible process.

Confirmation of a clinical diagnosis of OLP by means of histopathological study of a biopsy specimen is generally advised. As hardly any data exist about the correlation between clinical and histopathological diagnoses of OLP, the degree of this correlation was studied in **chapter 4.** In 42% of the cases of which all clinicians agreed about the clinical diagnosis being diagnostic of OLP there was no consensus on the histopathological diagnosis. Conversely, in 50% of the cases of which all pathologists agreed about the histopathological diagnosis being diagnostic of OLP there was a lack of consensus on the clinical diagnosis. Based on these findings there appears to be a lack of clinicopathological correlation in the diagnostic assessment of OLP. A proposal for a set of revised diagnostic criteria of OLP and OLL, based on the WHO definition of OLP, including clinical as well as histopathological aspects, was therefore made.

Chapter 5 describes the possible premalignant character of OLP and OLL of a prospectively followed cohort of patients with detailed documentary data applying the proposed revised criteria of OLP and OLL as described in chapter 4. A study group of 173 patients, 62 patients diagnosed with OLP and 111 patients with OLL, was followed for periods ranging from 6.6 – 72.0 months, with a mean of 31.9 months. Three out of 173 patients (1.7%), two men and one woman, developed a squamous cell carcinoma of the oral mucosa during follow-up. All malignant transformations occurred in the OLL group. The annual malignant transformation, based on a mean follow-up of 31.9 months, was calculated at 0.65 % per year. A comparison of the expected against actual figures for developing carcinomas showed no increase in OLP patients and a 219-fold increase in OLL patients, the latter being statistically not significant, but with a p-value of 0.083 suggesting at least a trend. These results give some support to the hypothesis that OLL are of a premalignant nature. Classical cases of OLP, clinically as well as histopathologically evident OLP, are probably innocuous. Before a final statement with regard to the premalignant character of OLP and OLL can be formulated the present follow-up study should be prolonged and expanded with a larger number of patients. Until then, we advise to offer patients with OLP and OLL bi-annual follow-up examination.

In **chapter 6** costs and effectiveness of screening for oral cancer in OLP patients were calculated with a decision model. Besides, the cost-effectiveness of different screening scenarios were compared, and a sensitivity analysis of several variables used in this model was performed. The health gain from screening was 592 quality adjusted live years (QALY's) or the equivalent of 23.68 lives saved costing 1,265,229 dollar, meaning that one equivalent live saved (ELS) costed 53,430 dollar. Increase of cancer treatment costs will significantly decrease the costs per ELS. When the malignant transformation rate (MTR) is lower than 0.4 per cent per year extra costs per ELS will increase exponentially. The effect of sensitivity and specificity of an oral examination in detecting oral cancer on cost-effectiveness seems to be substantial. When the proportion of cancers found in stage I can be increased from 40% (without screening) up to at least 60% after screening extra costs per ELS will decrease exponentially.
Screening for oral cancer in OLP patients, based on the presently used model, seems attractive. However, varying the several variables in the decision model has a significant impact on the final costs and effectiveness. It was emphasized that, only, when additional information about these variables will become available, a more precise and realistic calculation can be performed.

SAMENVATTING

Reeds enkele decennia is er een wetenschappelijke discussie gaande over het mogelijke premaligne karakter van lichen planus van het mondslijmvlies (OLP). Enkele tientallen klinisch-pathologische follow-up studies, het merendeel van retrospectieve aard, beschrijven een maligne transformatie percentage dat varieert van 0.04 – 1.74 % op jaarbasis. Uitgaande van deze gegevens beschouwt een aantal wetenschappers OLP als een premaligne conditie; dat betekent dat OLP geassocieerd zou zijn met een significant verhoogd risico op het ontwikkelen van een maligniteit van de mondholte. Het hanteren van wisselende inclusiecriteria in de hierboven genoemde follow-up studies is de belangrijkste oorzaak van kritiek op deze stellingname. Er bestaan namelijk geen algemeen geaccepteerde diagnostische criteria voor OLP. Daarnaast geven klinisch en histopathologisch diagnostische criteria van OLP, zoals geformuleerd door de Wereldgezondheidsorganisatie (1978), ruimte voor subjectieve interpretatie. In dit proefschrift wordt het mogelijke premaligne karakter van OLP en lichenoïde afwijkingen van het mondslijmvlies (OLL) bestudeerd vanuit een klinisch-pathologisch perspectief.

In **hoofdstuk 1** wordt een overzicht gegeven van de klinisch-pathologische literatuur aangaande het mogelijk premaligne karakter van OLP van de periode 1977-1999. Gebaseerd op een literatuuroverzicht van de periode 1950-1976 zetten Krutchkoff e.a. hun vraagtekens bij het mogelijk premaligne karakter van OLP. Hun kritiek bestond met name uit de onvolledige beschrijving van de oorspronkelijke diagnostische gegevens van de patiënten met OLP die op de lange termijn een maligniteit ontwikkelden. In het huidige literatuuroverzicht, waarbij dezelfde criteria werden toegepast als die van Krutchkoff e.a., werden 33 van de 98 (34%) beschreven gevallen geaccepteerd als voldoende bewijs voor maligne ontaarding van een patiënt met OLP. Hoewel dit percentage hoger bleek dan destijds beschreven door Krutchkoff e.a. wordt geconcludeerd dat er ontegenzeggelijk behoefte bestaat aan algemeen geaccepteerde en gevalideerde diagnostische criteria voor OLP.

In **hoofdstuk 2 en 3** wordt de betrouwbaarheid van de klinische en histopathologische definitie van OLP, zoals destijds in 1978 geformuleerd door de Wereldgezondheidsorganisatie, onderzocht. Hiertoe werden de interobserver en intraobserver variabiliteit bepaald middels het berekenen van kappa-waarden. De interobserver overeenstemming bij het vaststellen van de klinische diagnose bleek

hierbij matig tot voldoende, terwijl de interobserver overeenstemming bij de histopathologische diagnostiek slecht tot matig bleek. De intraobserver overeenstemming was bij zowel de klinische, als bij de histopathologische diagnostiek significant beter. De resultaten van deze studie suggereren dat het stellen van de diagnose OLP, uitgaande van de definitie van de Wereldgezondheidsorganisatie, veelal subjectief en onvoldoende reproduceerbaar is.

Bevestiging van een klinische diagnose OLP middels het verrichten van een proefexcisie wordt over het algemeen geadviseerd. Er zijn echter nauwelijks gegevens voorhanden over de correlatie tussen de klinische en histopathologische diagnose OLP. De mate van correlatie werd daarom bestudeerd en beschreven in **hoofdstuk 4**. In 42% van de gevallen waarin clinici het eens waren over de klinische diagnose OLP bestond geen consensus over de histopathologische diagnose. Daarentegen was in 50% van de gevallen waarin oraal pathologen het eens waren over de histopathologische diagnose OLP geen overeenstemming over de klinische diagnose. De correlatie tussen het klinische en het histopathologische beeld van OLP is derhalve matig. Een voorstel voor gereviseerde diagnostische criteria voor OLP en OLL, uitgaande van de huidige definitie van de Wereldgezondheidsorganisatie, werd daarom geformuleerd. Deze criteria omvatten zowel klinische als histopathologische aspecten.

Hoofdstuk 5 beschrijft het mogelijk premaligne karakter van OLP en OLL aan de hand van een prospectief gevolgd cohort patiënten met OLP en OLL. Bij de inclusie van patiënten werd gebruik gemaakt van de voorgestelde gereviseerde diagnostische criteria voor OLP en OLL zoals beschreven in hoofdstuk 4. De onderzoeksgroep van 173 patiënten, bestaande uit 62 patiënten met OLP en 111 patiënten met OLL, werd gedurende een gemiddelde periode van 31.9 maanden gevolgd. Drie patiënten (1.7%) ontwikkelden tijdens de follow-up een plaveiselcelcarcinoom van het mondslijmvlies. Alle maligne transformaties manifesteerden zich in de subgroep van de OLL patiënten. Uitgaande van een gemiddelde follow-up van 31.9 maanden werd een maligne transformatie percentage van 0.65% op jaarbasis berekend. Deze gegevens werden vervolgens vergeleken met de verwachte kans op de ontwikkeling van een mondholtecarcinoom in een vergelijkbare, voor leeftijd en geslacht gecorrigeerde, groep. Alhoewel de kans op de ontwikkeling van een mondholtecarcinoom bij OLP patiënten hierbij niet

verhoogd was, bleek deze kans bij OLL patiënten 219 maal verhoogd. Deze resultaten geven enige ondersteuning aan het mogelijk premaligne karakter van OLL. 'Klassieke' OLP, waarbij zowel klinisch als histopathologisch voldaan wordt aan de gereviseerde criteria voor OLP, is vermoedelijk een onschuldige aandoening. Om te komen tot een definitieve uitspraak over het mogelijk premaligne karakter van OLP en OLL dient de huidige onderzoeksgroep te worden uitgebreid en langer te worden gevolgd. Voorlopig wordt geadviseerd patiënten met OLP en OLL twee maal per jaar te controleren.

In **hoofdstuk 6** worden kosten en effectiviteit van de screening van patiënten met OLP op de aanwezigheid van een mondholtecarcinoom berekend aan de hand van een model. Tevens wordt de kosten-effectiviteit van verschillende screeningsscenario's vergeleken en wordt een sensitiviteitsanalyse verricht van de verschillende variabelen welke voorkomen in het model. De opbrengst van screening bleek 592 quality adjusted live years (QALY's), equivalent aan 23,68 gewonnen levens (ELS). De met screening gepaard gaande kosten bedroegen 1.265.229 dollar, overeenkomend met 53.430 dollar per ELS. Bij stijgende behandelingskosten van kanker daalden de kosten per ELS significant. Daling van het maligne transformatie percentage beneden 0,4% op jaarbasis deed de extra kosten per ELS exponentieel toenemen. Wijziging van de sensitiviteit en/of specificiteit van een mondonderzoek bij de opsporing van een mondholtecarcinoom had een substantieel effect op de kosten-effectiviteit. Indien door screening het aantal stadium I tumoren werd verhoogd van 40% (zonder screening) naar 60% (met screening) bleken de kosten per ELS exponentieel te dalen. Gebaseerd op het huidige model lijkt screening voor de vroege opsporing van het mondholtecarcinoom bij OLP patiënten aantrekkelijk. Wijziging van de diverse variabelen welke voorkomen in het model heeft een significante invloed op de uiteindelijke kosten-effectiviteit. Slechts indien aanvullende informatie aangaande deze variabelen vrijkomt, is een meer exacte en dus ook de realiteit meer benaderende berekening mogelijk.

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Erik

De auteur van dit proefschrift werd geboren op 24 augustus 1970 te Ede. In 1988 behaalde hij zijn eindexamen VWO aan het Christelijk Streek Lyceum Ede. Datzelfde jaar werd begonnen met de studie tandheelkunde aan het Academisch Centrum Tandheelkunde Amsterdam (ACTA). Zowel het propedeutisch (1989) als doctoraal examen (1993) werden 'cum laude' afgesloten, waarna in 1994 het tandartsexamen werd behaald. Aansluitend werd een jaar doorgebracht in Vancouver, Canada, alwaar aan de British Columbia Cancer Agency een fellowship Oral Medicine werd gevolgd onder begeleiding van prof. dr. J.B. Epstein. Na terugkomst uit Canada werd in 1995 gestart met de studie geneeskunde aan de Vrije Universiteit te Amsterdam. Gelijktijdig werd een aanvang gemaakt met het promotieonderzoek op de afdeling Mondziekten en Kaakchirurgie/Orale Pathologie, Vrije Universiteit/ACTA te Amsterdam (hoofd: prof. dr. I. van der Waal). In 2000 werd het doctoraal examen geneeskunde behaald; het artsexamen werd afgerond in 2002. Sinds 1 juli 2002 is hij in opleiding tot specialist in de Mondziekten en Kaakchirurgie (opleider: prof. dr. I. van der Waal).

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