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ORIGINAL ARTICLE

Malignant transformation of oral leukoplakia: a follow-up study

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Abstract

Objective The main objective of the study was to identify the determinants that contribute to the malignant transformation of oral leukoplakia in a group of patients managed in secondary care. A secondary objective was to compare two dysplasia grading systems to determine their utility in assessing the prognosis.

Material and methods The cohort consisted of 93 patients diagnosed during the period 2009–2013. The variables recorded and analysed included age and sex, clinical presentation (colour) and severity of oral epithelial dysplasia (OED) scored by the WHO (2005) and the binary grading systems. The planned management included excision of high-grade dysplasia and observation of low-grade dysplasia lesions based on the WHO grading system. Patient factors were transcribed from the pathology records and updated using a questionnaire sent out to the whole group of patients. Data were analysed using χ^2 test and Kaplan-Meier analysis ($P < 0.05$).

Results Complete follow-up data were available for 93 patients. Malignant transformation occurred in 7 patients (7.5%) during a mean follow-up period of 30 months. Among the surgically excised group ($n = 51$), a recurrence of oral leukoplakia was noted in 16 patients (31%). WHO OED grading ($P = 0.02$) and the presence of red areas ($P = 0.012$) were useful in predicting malignant transformation with severe epithelial dysplastic lesions and red and white mixed lesions showing higher rates.

Conclusion Leukoplakias (7.5%) transformed over a mean follow-up period of 30 months. Dysplasia grading and the clinical appearance by colour (mixed white and red) were significant predictors of malignant transformation

Clinical significance Patients with erythroleukoplakia and those diagnosed with moderate or severe epithelial dysplasia require more intensive interventions as such lesions have a higher risk of developing a malignancy.

Keywords Oral leukoplakia · Oral epithelial dysplasia · Outcome · Malignant transformation

Introduction

Oral leukoplakia (OL) is defined by the World Health Organization (WHO) as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" [1]. OL is a clinical term, under which two main clinical subtypes have been described, namely homogenous and non-homogenous leukoplakia. Non-homogeneous leukoplakia carries a much higher risk of malignant transformation compared to the homogenous type [2, 3]. Tobacco smoking, smokeless tobacco and betel quid chewing have been established as main aetiological factors for the development of OL in over 75% of the affected individuals [4]. A leukoplakia that develops in a patient with no known risk factors is termed an idiopathic leukoplakia [5].

Although the natural history of OL and malignant potential of this disorder had been discussed widely in literature [6], methods of assessing the risk remain imprecise [3]. Based on reported follow-up data in observational studies, malignant transformation of OL may range from 0.13 to 34.0% [7–20]. Factors associated with the risk for malignant transformation seem to vary and may depend on the study population. In 2009, Van der Waal et al. listed the risk factors for malignant transformation in OL, namely gender (female), long duration, OL in non-smokers, location (tongue and the floor of the mouth), size of the lesion (over 200 mm^2), type of the lesion

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(non-homogenous appearance), presence of *Candida albicans* and presence of oral epithelial dysplasia (OED) in a biopsy [21]. A systematic review published later confirmed these findings [7]. Of all the known risk factors, the grade of dysplasia is considered by many as the strongest independent predictor of malignant transformation [10, 16]. At presentation, OL may be divided into high risk and low-risk lesions based on a combination of factors. As leukoplakia remains a provisional clinical diagnosis, a biopsy is undertaken to confirm the diagnosis, to assess the severity of dysplasia and to exclude malignancy [3]. In dysplastic oral leukoplakia, malignant transformation could be close to 40% [22]. In Sri Lanka, as per National Guidelines [23], a leukoplakia with a higher grade of dysplasia is surgically excised while those with no dysplasia or mild dysplasia grading are followed up on the basis of a wait and watch policy with attention to habit intervention. However, the literature indicates the possibility of malignant transformation in both surgically treated and non-treated lesions [13], while a meta-analysis has shown that surgical excision may reduce the risk of malignant transformation [24]. Observational studies on OL have been limited, and those reported so far [8–19] provide somewhat contradictory outcomes.

The objectives of this study were to evaluate the outcome of a series of OLs and to identify risk factors associated with malignant transformation of oral leukoplakia. In addition, a secondary objective was to compare two dysplasia grading systems to determine their utility in assessing prognosis.

Materials and method

Three hundred patients with a clinical diagnosis of oral leukoplakia or erythroleukoplakia (based on WHO Collaborating Centre criteria—see [1]) confirmed with a biopsy and managed during the period from 2009 to 2013 were selected for the study. Out of a preliminary selection, 164 patients were excluded due to lack of complete clinical information. Ethical clearance for the study was obtained from the Ethical Review Committee of the Faculty of Dental Sciences, University of Peradeniya.

Data were extracted from medical/pathology records. A pre-tested questionnaire [25] was posted to all patients who were on follow-up to ascertain any missing data. For the protection of confidentiality of the patient's personnel details, a unique accession number was given on data extraction questionnaires.

A total of 123 questionnaires were returned giving a response rate of 41%. However, 23 questionnaires had to be excluded due to incomplete information giving a sample size of 100. All patients included in the study had their pathology diagnoses reviewed by an experienced oral pathologist, and in 7 cases, excision biopsies had micro-invasive carcinomas and were excluded from the study. Thus, the malignant transformation rate was calculated for only 93 patients. Grading of epithelial dysplasia was undertaken based on the 3-grade WHO 2005 classification [26] and also by the binary grading system proposed by Kujan et al. [27], grouping cases to high-risk and low-risk dysplasia. Data were entered on the Excel programme and analysed with the Statistical Package for Social Science (IBM SPSS Statistics 20). Chi-square test was used at $P < 0.05$ significance to evaluate variables associated with malignant transformation and Kaplan-Meier analysis to obtain factors contributing to oral cancer-free survival.

Results

A total of 93 patients were eligible for the study with a complete data set. Table 1 shows the demographic features of patients diagnosed with OL. The majority of patients (75.3%) were over 50 years of age at the time of diagnosis with a male predilection (78.5%). Further, approximately two-thirds of the sample composed of individuals of low socioeconomic status as determined by their income, level of education and occupation. By anatomical site, 70.9% of the leukoplakias

Table 1 Demographic characteristics of the study population

Demographic characteristic	Frequency (%)
Age in years	
< 50	23 (24.7)
≥ 50	70 (75.3)
Gender	
Male	73 (78.5)
Female	20 (21.5)
SES by occupation	
Blue collar workers + farmers	30 (32.3)
Pink collar workers	14 (15.0)
White collar workers	1 (01.1)
Unemployed/retired	25 (26.9)
Not given	23 (24.7)
SES by income	
Low	44 (47.3)
Middle	35 (37.6)
High	2 (02.2)
Not given	12 (12.9)
SES by education	
Illiterate	5 (05.4)
Primary education	36 (38.7)
Secondary education	23 (24.7)
University education	5 (05.4)
Not given	28 (30.1)

SES socioeconomic status

occurred on the buccal mucosa while 23.6% were on the lateral tongue and floor of the mouth.

Eleven (11.82%) patients did not admit to having any major risk habits. Eight out of 11 without any risk habits were females. Among those with risk habits, 70 (75.3%) were betel quid chewers. Thirty-seven (39.8%) were smokers and 36 (38.7%) were alcohol users. Out of the 82 patients who practiced risk habits, 17 (20.7%) practiced all three risk habits; these were all males. Moreover, 4 (4.87%) males admitted to using alcohol only.

Among the 93 cases of OL, incisional biopsies revealed that 20 had keratosis without epithelial dysplasia and 34 had keratosis with mild epithelial dysplasia. The remaining 20 and 19 cases were diagnosed as keratosis with moderate and severe epithelial dysplasia respectively. Treatment by surgical excision by dysplasia grade is given in Table 2. All with severe epithelial dysplasia and 20–53% of other dysplastic grades were surgically excised.

During a mean follow-up period of 30 months (10–72 months), seven patients presented with oral squamous cell carcinoma (OSCC) confirmed in a subsequent biopsy. Malignant transformation for the total sample was estimated at 7.52%. Out of the seven patients who developed OSCC, two patients died due to the disease.

Table 3 shows the factors predicting malignant transformation. It must be noted that our estimates are based on a small sample of 7 subjects who developed malignancy. WHO OED grading ($P = 0.02$) and clinical presentation by colour ($P = 0.012$) were significant in predicting malignant transformation; severe epithelial dysplastic lesions and red and white mixed lesions (non-homogenous OL) showed higher ratios of transformation. There was no statistically significant association between malignant transformation with age at presentation, gender, site or habits. Figure 1 shows the cancer-free survival over the follow-up period. Severe OED correlated with the worst survival compared with other grades of dysplasia (log-rank $P = 0.01$). Binary grading was less discriminatory in survival analysis ($P > 0.052$) (Fig. 2). Again, it must be noted that the above analysis is based on our small sample of 7 subjects who later developed cancer during the follow-up.

During the follow-up period, 7 (7.5%) developed a second primary leukoplakia. Four (50%) occured in opposing sides of the buccal mucosa, and 4/7 second primary lesions were in patients who were initially diagnosed with 3 severe, 1 moderate and 3 mild OED.

Table 4 shows the mean time taken to develop a recurrence following surgical excision and to develop a second primary lesion or OSCC. Sixteen (31%) of OL that were surgically excised developed recurrences. Most of the recurrences (11/16; 68.6%), developed in leukoplakias, were initially diagnosed with severe OED. When evaluating the excisional biopsy reports, it was found that none of these leukoplakias was incompletely excised, though 3 lesions had mild dysplasia at their excision margins. Further, time taken for the development of recurrences in mild OED and severe OED was 43.6 and 23.5 months respectively. Time taken for the development of a second primary leukoplakia among patients diagnosed with mild OED was 43 months, while it only took approximately half the time to develop second primaries in patients diagnosed with moderate or severe OED. No clear distinction could be observed in the time for malignant transformation among the different subgroups (Table 4).

Discussion

Though the prevalence of oral potentially malignant disorders is reported to be higher in Southeast Asia [28], follow-up studies reported in the literature from this region are meager. In this study, we examined the outcome in 93 patients with oral leukoplakia managed in secondary care facilities. Our study has strengths as the clinical diagnosis was based on WHO Collaborating Centre Criteria [1], their histopathological diagnosis was confirmed following a biopsy and the presence of dysplasia was assessed using two grading systems [26, 27]. Follow-up information that was available in the pathology records were updated using a questionnaire sent out to all patients on our pathology record database. This approach allowed us to improve the cohort size on whom complete follow-up information was available for the study. Difficulty in collecting adequate follow-up information has been a limitation in reporting the natural history of oral leukoplakia in this region. Two dysplasia grading systems, the WHO 2005 grading system and the binary grading system, were used to assess the severity of dysplasia (26,27). As recommended in the reported evidence-based guidelines, the management was based on the severity of dysplasia with high-risk lesions being excised and the rest followed up at regular intervals with an intention to treat, if any changes were noted. However, in clinical practice, it is not possible to strictly follow this

Table 2 Management by dysplasia groups

Management	No ED (%)	Mild ED (%)	Moderate ED (%)	Severe ED (%)
Surgically excised	4 (20)	18 (53)	10 (50)	19 (100)
Wait and see	16 (80)	16 (47)	10 (50)	00
Total	20 (100)	34 (100)	20 (100)	19 (100)

Table 3 Clinico-pathological features of OL with and without malignant transformation

Feature		Developed cancer (%)	No cancer (%)	Total	χ^2 test
Age in years	≤ 50	1 (1.07)	26 (27.95)	27 (29.05)	$P = 0.37$
	> 50	6 (6.44)	60 (64.51)	66 (70.95)	
Gender	Male	4 (4.03)	69 (74.19)	73 (78.22)	$P = 0.15$
	Female	3 (3.22)	17(18.27)	20 (21.49)	
Site	Buccal mucosa	5 (5.37)	61 (65.59)	66 (70.96)	$P = 0.46$
	Tongue or FOM	1 (1.07)	21 (22.58)	22 (23.65)	
	Other	1 (1.07)	4 (4.03)	5 (5.10)	
Any habit†	Present	6 (6.45)	76 (81.72)	82 (88.17)	$P = 0.83$
	Absent	1 (1.07)	10 (10.76)	11 (11.83)	
Clinical presentation	White only	1 (1.07)	54 (58.06)	55 (59.13)	$P = 0.012$
	Red and white	6 (6.44)	32 (34.04)	38 (40.48)	
WHO dysplasia grading	No dysplasia	0	20 (21.50)	20 (21.50)	$P = 0.02$
	Mild OED	1 (1.07)	33 (35.48)	34 (36.55)	
	Moderate OED	1 (1.07)	19 (20.43)	20 (21.50)	
	Severe OED	5 (5.37)	14 (15.05)	19 (20.42)	
Binary grading‡	Low risk dysplasia	1 (1.36)	33 (35.48)	34 (36.84)	$P = 0.07$
	High risk dysplasia	6 (8.21)	33 (35.48)	39 (43.69)	
Surgical excision	Yes	6 (6.45)	45 (48.38)	51 (54.83)	$P = 0.08$
	No	1 (1.36)	41 (44.08)	42 (45.16)	
Outcome	Alive	5 (5.37)	85 (91.39)	90 (97.96)	$P = 0.000$
	Dead	2 (2.15)	1 (1.07)	3 (3.12)	

FOM floor of the mouth, *OED* oral epithelial dysplasia

† Habits included smoking, alcohol use and smokeless tobacco use or betel quid use

‡ Total sample size for binary grading is 73

guideline based on the pathologist's grading as some patients with moderate dysplasia may decline surgical treatment and some with even mild or no dysplasia may opt for surgical intervention. Furthermore, a leukoplakia with mild dysplasia presenting at a high-risk site, e.g. lateral margin of tongue or floor mouth, may be considered for excision by the operating surgeon. All patients in our series received habit intervention at the first presentation and during follow-up. Active

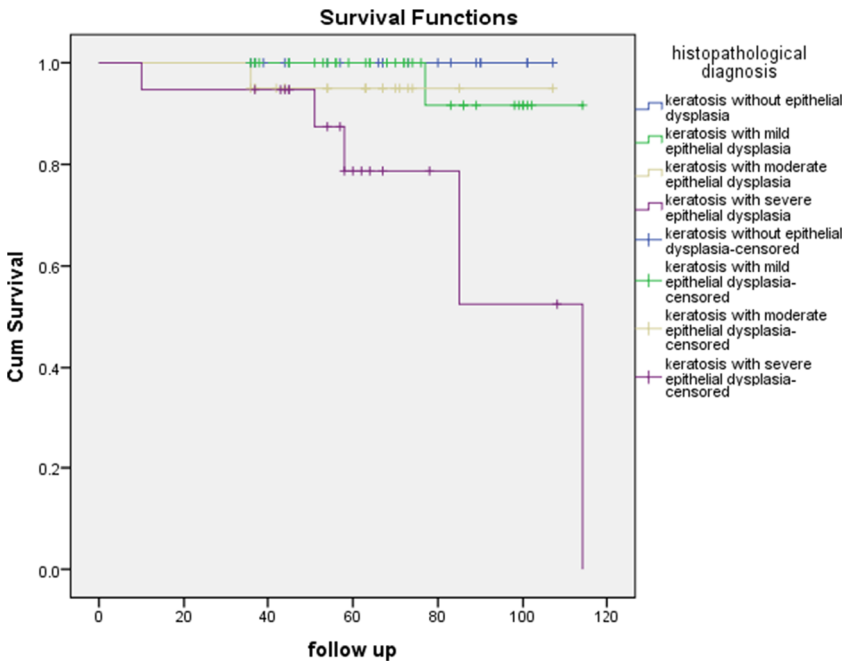

Fig. 1 Kaplan-Meier survival curves showing OSCC-free survival based on WHO dysplasia grading, Follow-up given in months, $P = 0.01$

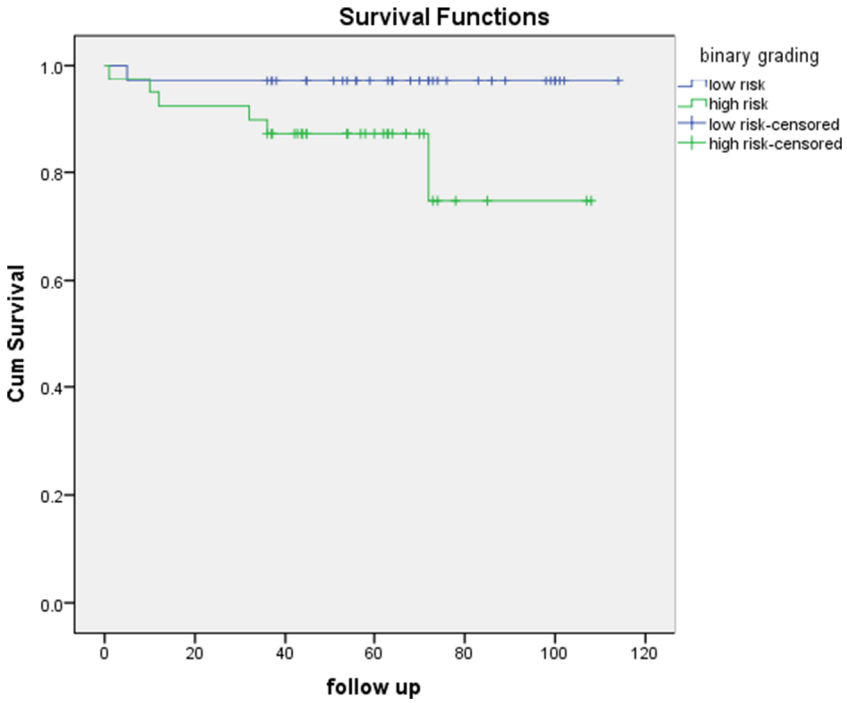

Fig. 2 Kaplan-Meier survival curve for OSCC-free survival based on binary grading of dysplasia, $P = 0.052$

intervention or a passive management policy for oral leukoplakia has been adopted in earlier reported studies (10, 19), and the available evidence was reviewed by Kumar et al. [29]. A Cochrane Review noted that leukoplakia in either group may transform to malignancy [30].

Among demographic variables, age and gender are considered for stratifying the risk of oral leukoplakia [3, 21]. We noted a male preponderance with a male/female ratio 3.5:1 in the whole group that is consistent with reported data from the region due to prevalent tobacco and betel quid habits. However, there was no statistical difference in the frequency of transformation with respect to gender ($P = 0.15$). Reviews of observational studies report that female gender has a higher risk in transformation [3, 7, 21] mostly based on European data, but this was not observed in our study. Age at presentation also was not significant for transformation of leukoplakia ($P = 0.37$). In some studies, a large size of the lesion (> 200 mm^2) is reported as a predictor of malignant transformation [13, 19], but we did not include size in our investigation.

Non-homogeneous leukoplakia could clinically present as erythroleukoplakia, nodular or verrucous types [1]. The erythroleukoplakia variety with red areas is mostly reported from European studies, but nodular and verrucous varieties are often found in South Asia due to prevalent smokeless tobacco habits [31]. Forty percent of oral leukoplakias recorded in this study had a non-homogenous appearance, highest recorded so far in any case series of oral leukoplakia. Silverman et al. [9] initially reported from the USA a higher malignant transformation rate in non-homogenous varieties compared with homogeneous variety that appears uniformly white [9]. In our study, six out seven leukoplakias that transformed had a red and white appearance at presentation consistent with a diagnosis of erythroleukoplakia, providing clear evidence that malignant transformation was significantly higher in erythroleukoplakia ($P = 0.012$). The red appearance in a leukoplakia could be due to atrophy of the surface epithelium or due to increased vascularity of the submucosa [31]; both atrophy and increased stromal vascularity biologically have a predisposition to malignancy [32]. Other clinical

Table 4 The mean time taken for the development of recurrences, second primary lesions of OL or carcinoma

Pathological diagnosis of the primary lesion	Recurrence of leukoplakia at the site of excision		Second primary leukoplakia at another site		Carcinoma	
	No	Time	No	Time	No	Time
Mild dysplasia	5	43.6 (6–60)	3	43 (33–54)	1	24
Moderate or severe dysplasia	11	23.54 (4–67)	4	21.2 (11–70)	6	30.6 (10–72)

The mean time given in months (range in parenthesis)

features such as size of the lesion or the duration of the lesion mentioned as predicting the malignant transformation by Van der Waal [21] could not be analysed in the present study due to lack of reliable information. Female gender, the anatomical site and idiopathic OL mentioned by Van der Waal [21] were also not significantly associated with malignant transformation in the present study. The severity of oral epithelial dysplasia is currently used as the gold standard for predicting malignant transformation in oral leukoplakia [31]. This guideline is based on the evidence from several observational studies reported in the literature [10, 16]. A meta-analysis reported higher risk of developing malignancy in dysplastic lesions [24], though not all authors agree that dysplasia recording provides a clear risk stratification guide for clinicians to manage oral leukoplakia [20]. In this study, we used two systems to grade dysplasia: the WHO 2005 system that allows a three-tier grading [26] and the binary system introduced by Kujan et al. [27] that classifies leukoplakia lesions as low or high risk. An expert group who met at the WHO recently recommended that the binary system could be used in pathology reporting in order to provide additional and clearer information to the clinicians [33, 34]. In our study, there was more or less equal distribution of cases when examined by the three grades, with some skewing to the mild dysplasia grade. However, by the binary grading system, more cases were grouped in the high-risk grade (44% vs 37%). The malignant transformation was significantly higher in the severe dysplasia group (5.37%) while in other grades, only 1% transformed ($P = 0.02$). Follow-up data analysed by Kaplan-Meier survival analysis (Figs. 1 and 2) found both dysplasia grades stratified the risk of malignancy, with higher risk grades showing a significantly higher malignant transformation. Statistical differences noted in the ability of the two grading systems to discriminate the risk should be viewed with caution due to small sample sizes. Dysplasia grading in the original biopsy was also significantly associated with cancer-free survival. There is much controversy on the utility of dysplasia grading to stratify the risk of oral leukoplakia. In a systematic review of 5 observational studies that statistically analysed dysplasia grading, 3 studies reported significant findings of dysplasia grading being effective for future prediction of malignant transformation [7]. More recently, the ploidy status, loss of heterozygosity and biomarkers have been researched to assess the risk prediction of oral potentially malignant disorders. The presence of aneuploidy in a leukoplakia has been reported to offer good discrimination to assess the risk of malignancy [35]. The World Workshop on Oral Medicine V11 reported that biomarker studies have failed to identify a single or a panel of biomarkers with any predictive value for management of leukoplakia and to continue the use of dysplasia grading for treatment planning of oral leukoplakia [36].

We also investigated several other parameters such a time to transformation, frequency of recurrence of surgically resected leukoplakias or the development of second primary lesions. There is dearth of information on these factors in the literature to compare our data. Moreover, the numbers in our study on these secondary data were too small to make generalizations from our study. Our data support the use of review protocols to follow-up patients at least for 5 years following their first presentation.

Conclusions

Leukoplakias (7.5%) transformed over a mean follow-up period of 30 months. Dysplasia grading and the clinical appearance based on colour (non-homogenous leukoplakia presenting as mixed white and red lesions) were significant predictors of malignant transformation. WHO 2005 dysplasia grading system predicted malignant transformation. Based on our data, validation of the two dysplasia grading systems using a larger sample is recommended for future studies.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Primali Jayasooriya, Kitmini Dayaratne and Upul Bandara Dissanayake. The first draft of the manuscript was written by Primali Jayasooriya, and it was critically reviewed with corrections by Prof Saman Warnakulasooriya. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures (information gathered) in the study involving human participants were in accordance with the ethical standards of the institution (Faculty of Dental Sciences, University of Peradeniya) and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from individuals included in the study at the time that questionnaires were posted to gather follow-up data.

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