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Review Article

Oral Leukoplakia Related to Malignant Transformation

Teruo Amagasa, Masashi Yamashiro and Hitoshi Ishikawa

Maxillofacial Surgery, Graduate School, Tokyo Medical and Dental University
(Chief: Professor Teruo Amagasa)

Abstract: Oral leukoplakia and its malignant transformation are reviewed in this article. Oral leukoplakia is defined as a predominantly white lesion of the oral mucosa that can not be characterized as any other definable lesion; however, the lesion must be confirmed histopathologically by biopsy in order to discuss malignant transformation of oral leukoplakia. Malignant transformation rates of oral leukoplakia range from 0.13 to 17.5%, while the rates of five-year cumulative malignant transformation range from 1.2 to 14.5%. Some reports found a high incidence of malignant transformation in older patients. Chewing tobacco and smoking are distinct risk factors particularly among males in certain countries; however, other countries have noted that females or non-smokers may be at risk of malignant transformation. HPV has been detected in oral dysplasia lesions and cancer in non-smokers. Conflicting reports have been presented regarding the malignant transformation of oral leukoplakia with epithelial dysplasia; however, we and some authors believe that epithelial dysplasia is an important factor in the malignant transformation of oral leukoplakia. The majority of researchers showed non-homogenous leukoplakia as a risk factor, although different terms have been used to describe these lesions. There may be several routes to malignant transformation of oral leukoplakia, including transformations induced by carcinogenesis due to betel quid chewing or smoking, or by HPV infection. While no definite treatment modalities for oral leukoplakia have been established, we suggest surgical therapy with an adequate safety-margin and well-timed evaluation as an appropriate treatment in preventing malignant transformation.

Key words: Oral leukoplakia, Malignant transformation, Epithelial dysplasia, Clinical type, Treatment

Introduction

The mortality rate due to cancer has continued to increase over the last 50 years in Japan. Within the last 25 years, carcinoma has become the leading cause of death in Japan, with the rate of people dying from oral and pharyngeal carcinoma increasing about 3-fold[1]. Since some types of cancer develop from precancerous lesions, early diagnosis and timely treatment of such precancerous lesions can prevent their malignant transformation. Oral leukoplakia is noted to be the most common premalignant lesion of the oral mucosa[2] and it is therefore important to clarify its clinical and histopathological characteristics. However, the mechanism of malignant transformation remains unknown. In this review, we focus on the relationship between the clinical and histopathological characteristics of oral leukoplakia and its malignant transformation.

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Requests for reprints: Teruo Amagasa, Maxillofacial Surgery, Graduate School, Tokyo Medical and Dental University, Yushima 1-chome, 5–45, Bunkyo-Ku, Tokyo 113–8549, Japan, Phone: +81–3–5803–5498, Fax: +81–3–5803–0198, E-mail: t-amagasa.mfs@tmd.ac.jp

Definition of oral leukoplakia

Oral leukoplakia is defined as a predominantly white lesion of the oral mucosa that can not be characterized

Table 1 Clinical classification of oral leukoplakia[8]

Type I :	flat, white patch/plaque without red components
Type II :	flat, white patch/plaque with erosion or red components
Type III :	slightly raised or elevated white patch/plaque
Type IV :	markedly raised or elevated white patch/plaque

We classified oral leukoplakia into 4 clinical types based on our experience.

as any other definable lesion[2,3]. This very broad definition has led a number of clinicians to report their own classification criteria, although the general concept and the essential substance of oral leukoplakia have remained unchanged for a long time[2–6]. Pindborg *et al.*[2] state that leukoplakia should be used only as a clinical term, and we assert that final diagnosis is confirmed histopathologically by biopsy. Lesions that are diagnosed histologically as cancer are to be excluded from cases of leukoplakia.

Clinical classification of oral leukoplakia

The clinical and histological aspects of oral leukoplakia were rarely reported prior to the findings of Pindborg *et al.*[7]. Axell *et al.*[3] and Pindborg *et al.*[2] classified homogenous and non-homogenous leukoplakias into 4 subtypes for each. Homogenous types were classified into flat, corrugated, wrinkled, and pumice types, whereas non-homogenous types were classified as verrucous, nodular (speckled), ulcerated, and erythroleukoplakia types. The pumice type of leukoplakia was mostly associated with tobacco smoking[38]. Generally, non-homogenous types are considered to show a greater risk of malignant transformation[2]. We previously classified oral leukoplakia into 4 clinical types[8]: type I, flat white patch or plaque without red component; type II, flat white patch or plaque with red components; type III, slightly raised or elevated white plaque; and type IV, markedly raised or elevated white plaque (Table 1, Fig. 1 (A–D). Fig. 2 (A–C) are representative examples of epithelial dysplasia we used in the studies[8,19,20,33,34].

Relationship between clinical classification of leukoplakia and epithelial dysplasia

Sharp[9], Rotter *et al.*[10] and Hahn *et al.*[11] reported that verrucous leukoplakia was often associated with epithelial dysplasia, and Ackermann and Johnson[12] and Shafer and Waldron[13] stated that a pinkish-gray or red granular appearance was often associated with epithelial dysplasia or carcinoma *in situ*. Pinborg *et al.*[7] confirmed that speckled leukoplakia, which is characterized by the presence of white patches in a nodular form or white lesions interspersed with erythematous area, was often associated with epithelial dysplasia or carcinoma. These findings were supported by subsequent reports showing the association of non-homogenous leukoplakia with epithelial dysplasia[14–16]. Sugár and Bánóczy[17], using a different clinical classification, also reported the association of leukoplakia erosiva and leukoplakia verrucosa with epithelial dysplasia. Because the clinical manifestations of oral leukoplakia in Japan did not exactly match these classification systems (there are few cases with nodular appearance in Japan), we constructed our own classification system[8], as mentioned above, in which type II oral leukoplakia included an ulcerated type or erythroleukoplakia[18]. We found that the occurrence of epithelial dysplasia was highly associated with type II leukoplakia, followed by type III or IV (Table 2)[19–20].

Malignant transformation rate versus cumulative malignant transformation rate

Previously reported rates of malignant transformation of oral leukoplakia range from 0.13 to 17.0% (Table 3)[18,20–33]. Our recent study showed that the malignant transformation rate of oral leukoplakia was 7.9% (35 of 444 patients with oral leukoplakia)[20]. However, the rate of malignant transformation may increase when patients are followed over a longer term or may decrease when patients are lost early to follow-up. The resulting rate of malignant transformation can therefore be unreliable. To eliminate this bias, the calculation of cumulative survival rate is necessary to determine the cumulative malignant transformation rate. The cumulative transformation rates reported by some researchers are shown in Table 4. The 5-year cumulative malignant transformation rate ranged from 1.2 to 14.5 %[25,32,34–37].

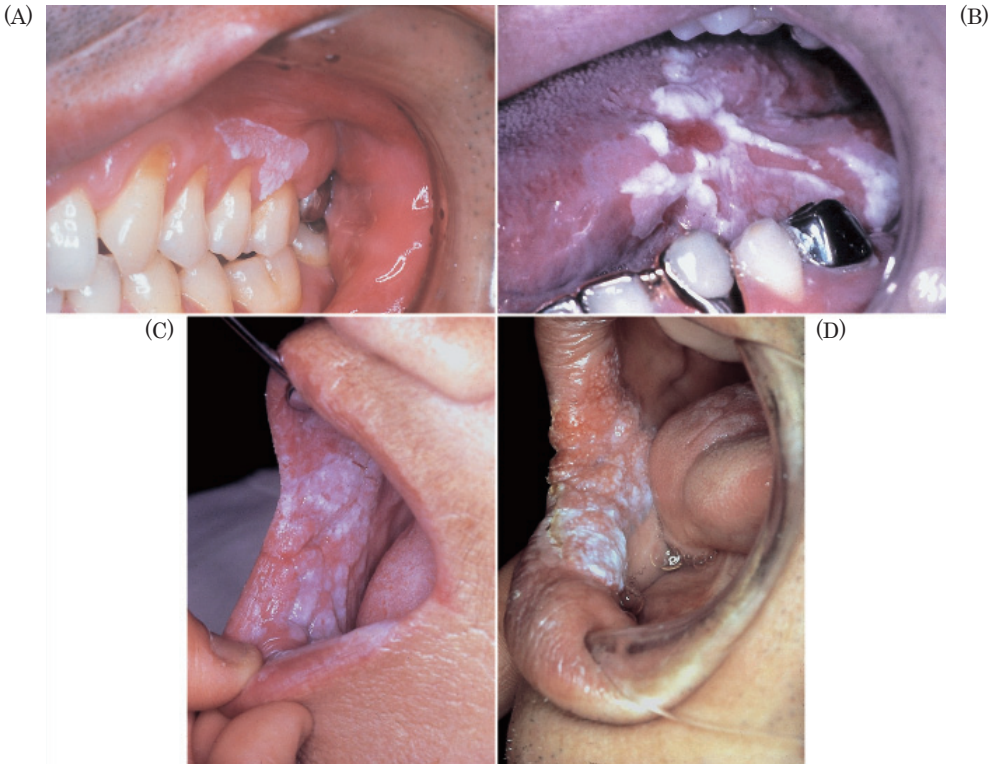

Fig. 1 Clinical features of leukoplakia can be classified into four types, type I (A) of the maxillary gingiva showing flat white patch, type II (B) of the tongue showing white patch and plaque with erosion, type III (C) of the buccal mucosa showing slightly elevated white plaque, and type IV (D) of the buccal mucosa showing markedly elevated white plaque with partly granular appearance.

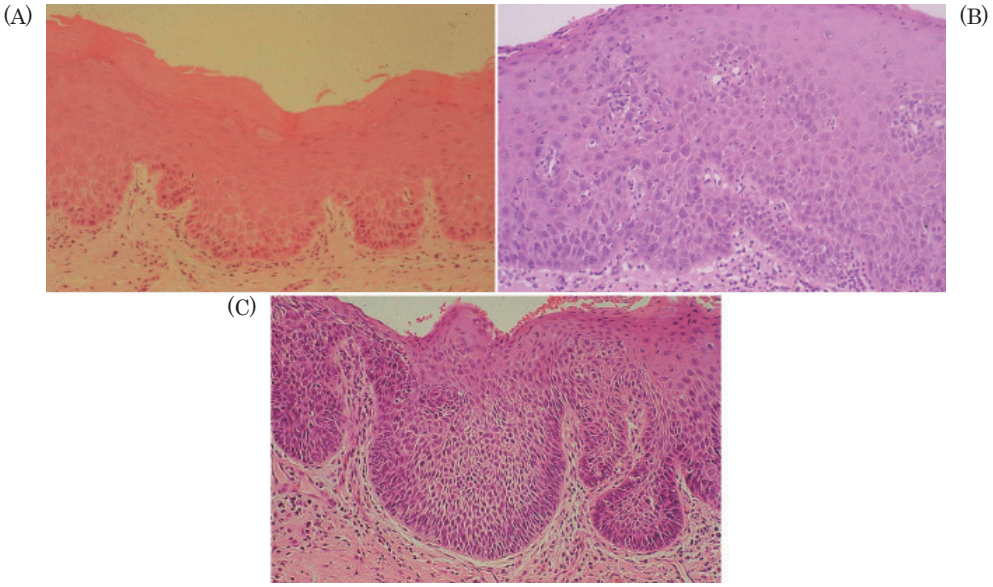

Fig. 2 Histopathological features of leukoplakia. Mild dysplasia (A): Slight irregular epithelial architecture limited to the lower third of the epithelium. Basal-parabasal cells show hyperchromatic large nuclei and loss of polarity. Moderate dysplasia (B): Hyperplastic epithelium with increased number of polymorphic cells extends up to two thirds of the epithelium, and cellular atypia is more pronounced with nuclear pleomorphism. Severe dysplasia (C): The atypical basal-like and spinous-like cells occupy almost all epithelial layers. Squamous epithelium is of variable thickness with drop-shaped rete ridges and prominent cytologic atypia.

Table 2 Incidence of epithelial dysplasia in each clinical type of oral leukoplakia[20]

Type	Cases	Non -dysplasia	Dysplasia			Total	No. of dysplasia (%)	
			Mild	Moderate	Severe			
I	328	203	86	30	9	125	(38.1)	*
II	71	13	31	16	11	58	(81.7)	*
III	24	11	10	2	1	13	(54.2)	
IV	21	7	11	1	2	14	(66.7)	
Total	444	234	138	49	23	210		
(%)		(52.7)	(31.1)	(11.0)	(5.2)		(47.3)	

*Statistically significant differences between incidence of epithelial dysplasia in type I and type II ($p<0.01$), and between type I and types II, III and IV ($p<0.01$).

Table 3 Malignant transformation of oral leukoplakia

Authors	Country	Year	No. of patients	Malignant transformation (%)	Observation periods (Years)
Silverman *et al.*[21]	India	1976	4762	0.13	2
Gupta *et al.*[22]	India	1980	360	0.3	1–10 (7)
Mehta *et al.*[23]	India	1972	117	0.8	10
Gupta *et al.*[22]	India	1980	410	2.2	1–10 (8)
Roed-Peterson *et al.*[24]	Denmark	1971	331	3.6	1– (4.3)
Einhorn *et al.*[25]	Sweden	1967	782	4.0	1–20
Pinborg *et al.*[26]	Denmark	1968	248	4.4	1– 9
Kramer *et al.*[27]	England	1969	187	4.8	1–16
Silverman *et al.*[28]	USA	1968	117	6.0	1–11
Bánócy[29]	Hungary	1977	670	6.0	1–30
Amagasa *et al.*[33]	Japan	1989	169	7.1	1–20
Amagasa *et al.*[20]	Japan	1999	444	7.9	1–29
Lind[30]	Norway	1987	157	8.9	6–
Gangadharan *et al.*[31]	England	1971	626	10.0	1–19
Schepman *et al.*[32]	Holland	1997	166	12.0	6M–17 (2.7)
Silverman *et al.*[18]	USA	1984	257	17.5	6M–39 (7.2)

Table 4 Cummulative malignant transformation rates of oral leukoplakia

Authors	(Year)	Country	No. of patients	5-year (%)	10-year (%)	Follow-up period (mean)
Einhorn *et al.*	(1967)[25]	USA	782	1.6	2.4	1–20y
Amagasa *et al.*	(1982)[33]	Japan	169	12.0	21.0	1–20y
Inoue *et al.*	(1985)[35]	Japan	75	4.5	9.7	7m-26y (12yr8m)
Kirita *et al.*	(1995)[36]	Japan	102	1.2	6.6	7m-12y1m (6y2m)
Schepman *et al.*	(1998)[32]	Netherlands	166	14.5	29.0	6m-16y9m【6y2m】
Kawabe *et al.*	(2001)[37]	Japan	237	4.7	11.1	(56.5 ± 43.4m)

【median】

Gender and malignant transformation

A large number of reports of oral leukoplakia, regardless of malignant transformation, identified a male predominance[13,16,17,20,21–23,28,29,31,38,39], with a female predominance reported in only a few[18,32,36].

Sex predilection for malignant transformation is unclear because of the conflicting data reported in the literature. Lind[30] reported that females were more prone

Table 5 Incidence of malignant transformation of oral leukoplakia according to sex and age[20]

Age	Male	Female	Total	(%)	
18–19	0/ 2	0/ 0	0/ 2	(0.0)	
20–29	0/ 12	1/ 7	1/ 19	(5.3)	
30–39	1/ 24	1/ 14	2/ 38	(5.3)	
40–49	1/ 52	1/ 34	2/ 86	(2.3)	*
50–59	6/ 90	6/ 58	12/148	(8.1)	
60–69	7/ 62	7/ 31	14/ 93	(15.1)	
70–79	1/ 29	1/ 23	2/ 52	(5.8)	
80	1/ 4	1/ 2	2/ 6	(33.0)	
Total	17/275	18/169	35/444		
(%)	(6.2)	(11.2)		(7.9)	

*Statistically significant difference of malignant transformation rate between the over 50-year-old group and the under 50-year-old group ($p<0.05$).

to undergo malignant transformation than males, and epithelial dysplasia was more frequent in females. This was further supported by the findings of other authors[26,28,29,32]. The risk factors for malignant transformation were listed by Schepman *et al*. (1998)[32] as follows: female gender, absence of smoking habits in women ($p<0.05$), and non-homogenous clinical aspect ($p<0.01$). However, other reports found a greater malignant transformation potential among males in India, particularly in association with chewing tobacco and smoking habits[21–23]. In our study, the malignant transformation rate (11.2%) of females with leukoplakia was higher than that (6.2%) of males (Table 5). However, this did not represent a significant statistical difference for gender[20].

Age and malignant transformation

Over a 30-year period, Bánóczy[29] identified a greater prevalence of leukoplakia among the 50–60 year-old group, but the risk of malignant transformation was highest among the 60–70 year-old group. Our study also showed a statistically significant difference of malignant transformation rate between the over 50-year-old group and the under 50-year-old group (Table 5)[20], supporting the findings of Chiesa *et al*.[40] with statistical significance. The relationship between higher malignant transformation rate and older patients may suggest that patients with longer exposure to oral leukoplakia are more prone to malignant transformation.

Site and malignant transformation

Our findings showed that the malignant transformation rate of oral leukoplakia of the tongue was significantly higher than that of the buccal mucosa and that of other sites (Table 6)[20]. These results concur with those of other studies conducted in Japan[35–37]. Some authors also reported that leukoplakia of the tongue and floor of the mouth exhibited a high risk of malignant transformation[24,41,42]. This is in contrast to other reports identifying the buccal mucosa and labial commissure as the areas with the highest malignant transformation rate, particularly for patients with tobacco chewing and smoking habits among Indian villagers[21,22,26]. On the other hand, some reports showed that no oral subsites are associated with a high risk of malignant transformation[32,43]. These differences might be related to the presence or absence of various oral habits of certain groups or populations.

Clinical type and malignant transformation

Since Pinborg *et al*.[7] showed that speckled leukoplakia was often associated with epithelial dysplasia and carcinoma, various reports about the correlation of the clinical type of oral leukoplakia with malignant transformation have been published[23,26,32,44,45]. Sugár and Bánóczy[17] reported that erosive leukoplakia showed the highest potential of malignant transformation in comparison to simplex leukoplakia. Holmstrup *et al*.[43] examined 236 patients with leukoplakia and using logistic regression analysis showed a 7-fold increase in the risk of malignant transformation (OR = 7.0) in non-homoge-

Table 6 Incidence of malignant transformation of 601 lesions of oral leukoplakias according to clinical type and site[20]

Site	I	II	III	IV	Total (%)
Tongue	8/ 93 (8.6)	14/40 (35.0)	0/ 6	2/ 7 (28.6)	24/143 (16.4)
Buccal	1/ 89 (1.1)	4/23 (17.4)	1/ 4 (25.0)	0/ 9	6/125 (4.8)
Lower gum	4/129 (3.1)	0/7	1/7 (14.3)	0/ 7	5/150 (3.3)
Upper gum	0/ 80	0/ 5	0/ 3	0/ 5	0/93 (0.0)
Palate	0/ 34	0/ 5	0/ 4	0/ 2	0/45 (0.0)
Floor of mouth	0/ 22	0/ 2	0/ 4		0/28 (0.0)
Lips	0/ 8	0/ 1	0/ 1		0/10 (0.0)
Oropharynx	0/ 3	0/ 1			0/ 4 (0.0)
Total	13/458 (2.8)	18/84 (21.4)	2/29 (6.9)	2/30 (6.7)	35/601 (5.8)

* Statistically significant differences of malignant transformation rate of leukoplakia between the tongue and buccal mucosa ($p<0.01$), and between the buccal mucosa and other sites ($p<0.01$). There were statistically significant differences between type II and type I ($p<0.01$), and between type II and types III and IV ($p<0.05$).

nous leukoplakia as compared to homogenous leukoplakia, and a 5.4-fold increase in the risk when the lesions exceeded 200 mm^2. In our classification, malignant transformation rate was the highest in type II lesions (21.4%), followed by type III (6.9%) and type IV (6.7%), with type I (2.8%) the lowest (Table 6)[20]. There were statistical differences between type II and type I, between type II and types III and IV, and between type I and types II, III and IV. However, there was no statistical difference between type I and types III and IV[20]. Despite the fact that various criteria are used to evaluate the clinical types of oral leukoplakia, we concur that leukoplakia with red components and the so-called nonhomogenous leukoplakia, including verrucous and raised type, carry a higher risk of malignant transformation.

Epithelial dysplasia and malignant transformation

The incidences of malignant transformation of oral leukoplakia with and without dysplasia are listed in Table 7[15,16,18,20,46–48]. Our study[20] showed that 28 (13.3%) of 210 patients having leukoplakia with epithelial dysplasia underwent malignant transformation, though only 7 (3.0%) of 234 patients with leukoplakia showing no epithelial dysplasia had malignant transformation. There was a statistical difference between the malignant transformation rate of the oral leukoplakia with epithelial dysplasia and that without dysplasia. However, there was no correlation between the malignant transformation rate and degree of epithelial dysplasia (Table 8)[20], because the leukoplakias with moderate and severe dysplasia were selectively and immediately excised. Some studies also showed that the malignant transformation rate of oral leukoplakia with epithelial dysplasia was higher than that of oral leukoplakia without epithelial dysplasia[18,48]. Kawabe *et al.*[37], using the Cox proportional hazard model, reported that only the presence of epithelial dysplasia and a previous history of oral cancer are significant predictors for the malignant transformation of leukoplakia.

On the contrary, Holmstrup *et al.*[43] reported that the presence of epithelial dysplasia in oral leukoplakia was not a statistically significant factor for malignant transformation based on logistic regression analysis. They described that this factor may, however, vary in levels of significance due to the subjectivity of diagnosis of epithelial dysplasia[49–51]

The periods from initial biopsy of oral leukoplakia to malignant transformation were examined in our study

Table 7 Malignant transformation rates of oral leukoplakia with and without dysplasia as reported in the literature

Authors	(Year)	No.of leukoplakia with epithelial dysplasia		No. of leukoplakia without epithelial dysplasia		Follow-up periods (yr)
		No. of cases	No. of malignat transformation (%)	No. of cases	No. of malignant transformation (%)	
Mincer *et al.*	(1972)[15]	45	5 (11.1)			Up to 8
Banoczy and Csiba	(1976)[16]	68	9 (13.2)			1–20 (mean 6.3)
Pindborg *et al.*	(1977)[46]	61	4 (6.6)			Up to 7
Silverman *et al.*	(1984)[18]	22	8 (36.4)	235	23 (9.8)	Mean 8.1
Lumerman *et al.*	(1995)[47]	44	7 (16.0)			Up to 6.5
Amagasa *et al.*	(1999)[20]	210	28 (13.3)	234	7 (3.0)	1–25
Cowan et al.	(2001)[48]	165	25 (15.0)	1182	12 (1.0)	over 20
Total		615	86 (13.9)	1651	42 (2.6)	

The malignant transformation rates of leukoplakia with dysplasia were higher than those without dysplasia.

Table 8 Incidence of malignant transformation of oral leukoplakias according to epithelial dysplasia[20]

Epithelial dysplasia	No. of cases	No. of malignant transformation (%)	
None	234	7 (3.0)	
Mild	138	18 (13.0)	*
Moderate	49	7 (14.3)	
Severe	23	3 (13.0)	
Total	444	35 (7.9)	

Table 9 Malignant transformation periods of 35 cases of oral leukoplakias according to epithelial dysplasia[20]

Epithelial dysplasia	Period (years)					
	≦ 2	≦ 5	≦ 7	≦ 10	10 <	Total
None	0	0	1	5	1	7
Mild	4	6	3	2	3	18
Moderate	1	4	2	0	0	7
Severe	1	2	0	0	0	3
Total	6	12	6	7	4	35
(%)	(17.2)	(34.3)	(17.1)	(20.0)	(11.4)	(100.0)

(Table 9)[20]. The shortest (less than 5 years) malignant transformation periods were observed for oral leukoplakia with severe dysplasia, followed by moderate epithelial dysplasia, mild dysplasia and no dysplasia from 5 years to a maximum 25 years 6 months. These findings suggest that there is a relationship between severity of epithelial dysplasia and the period of malignant transformation of oral leukoplakia to cancer development.

Etiologic factors of oral leukoplakia

The pathogenesis of oral leukoplakia is likely to be associated with oral habits since many studies showed a relationship of smoking with leukoplakia and malignant transformation[14,21,45,51]. A prospective epidemiologic house-to-house survey for randomly extracted samples in India showed that the annual incidence rate of leukoplakia was highest in the group with mixed tobacco habits (chewing and smoking) and was lowest in the group without any tobacco habits[52]. The rate of malig-

Table 10 Malignant transformation rates according to treatment[33]

Treatment	No. of cases	No. of malignant transformation (%)
Surgery	94	1 (1.1)
Chemotherapy	13	2 (15.4) *
Chemotherapy and surgery	13	1 (7.7) *
Radiation	5	1 (20.0)
None	44	7 (15.9)
Total	169	12 (7.1)

*Malignant transformation rate of leukoplakia treated by surgery was significantly lower than that without any treatment ($p<0.01$) or that without surgery ($p<0.01$).

nant transformation was also highest in oral leukoplakia associated with tobacco chewing habits. A case control study performed in Taiwan showed that adjusted odds ratios for betel nut chewing and smoking on the occurrence of leukoplakia were 17.43 (95% CI 1.94–1 56.27) and 3.22 (95% CI 1.06–9.78), respectively[53]. Moreover, the cessation of smoking is expected to reduce leukoplakia cases by 36%, while the elimination of betel nuts will prevent leukoplakia by 62% and malignant transformation to oral carcinoma by 26% in the underlying population[53].

Some authors have reported different findings, however. Schepman *et al.*[32] reported that the parameters associated with an increased risk of malignant transformation were female gender ($p<0.025$), absence of smoking habits in women ($p<0.05$), and a non-homogeneous clinical aspect ($p<0.01$). Silverman *et al.*[18] also showed that high risks for malignant transformation included non-smoking patients, the clinical presence of erythroplasia (erythroleukoplakia), and a clinical verrucous-papillary hyperkeratotic pattern.

Human papilloma virus (HPV) may also be implicated in oral leukoplakia as an infecting agent[54–60]. Compared with normal oral mucosa, HPV is detected frequently in oral dysplasia lesions and carcinoma, and HPV infection with a high-risk genotype is well known to be an independent risk factor for oral cancer[59]. The consistent absence of the malignant-type HPV in the betel quid-related lesions suggests that HPV plays only a minor role in betel quid-related carcinogenesis, although an association between the benign-type HPV with betel quid chewing may contribute to malignant transformation of oral mucosa[60].

From the above findings, it is suggested that there are several routes to malignant transformation of oral leukoplakia, including the transformations induced by the carcinogens in betel quid chewing and smoking, and by HPV infection. Further studies remain to be done.

Treatment

The lack of randomized controlled trials comparing the different treatment modalities for oral leukoplakia is a major dilemma for oral and maxillofacial surgeons. Several comparative studies have reported that there are no effective treatment procedures to prevent malignant transformation of oral leukoplakia[61–63]. The risk of cancer development could not be significantly reduced by surgical intervention[39,43,64,65]. The malignant transformation rates of oral leukoplakia appeared to be lower in the patients diagnosed by health examination in India who had no treatment as compared with in-patients[32]. Silverman *et al.*[21] found only 6 cases of malignant transformation in 4,762 patients with oral leukoplakia receiving no treatment over a 2-year period. Nevertheless, as our previous findings showed that the malignant transformation rate of leukoplakia treated by surgery was significantly lower than that without any treatment or that without surgery (Table 10), we believe that surgical excision with an adequate safety margin, coupled with well-timed evaluation of oral leukoplakia on follow-up, is effective in preventing the malignant transformation of these lesions[33]. Our findings are supported by some other reports[66,67].

Roodenburg *et al.*[68] treated oral leukoplakia of 70 patients with carbon dioxide laser evaporation and evaluated the outcome up to a 12-year period (mean 5.3 years). Most patients (90%) had no recurrence of oral leukoplakia and no malignant transformation was observed in any case. This is in support of one report[69] and in contrast to another[40]. Although vitamin A and

other retinoids[70] or topical bleomycin[71] are used for the therapy of leukoplakia, these were reported to have only a limited effect in controlling oral leukoplakia and in preventing malignant transformation.

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