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ORIGINAL ARTICLE

The value of regular follow-up of oral leukoplakia for early detection of malignant transformation

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Abstract

Objectives: Evaluate whether regular follow-up of oral leukoplakia (OL) resulted in early detection of malignant transformation (MT).

Method: Two hundred and twenty-two consecutive patients with OL (147 females, 75 males); median follow-up period of 64 months (range: 12–300). Three groups were distinguished: group A ($n = 92$) follow-up at the hospital; group B ($n = 84$) follow-up by their dentist; group C ($n = 46$) lost to follow-up.

Results: OLs in group B compared to group A, were smaller in size (<2 cm; $p < 0.001$), showed more hyperkeratosis ($p < 0.001$) and less moderate/severe dysplasia ($p < 0.001$). MT occurred in 45 (20%) patients: 32 (35%) in group A, five (6%) in group B and eight (17%) in group C. There was no significant difference in clinical tumour size between group A (median: 15 mm, range: 1–40) and group B (median: 10 mm, range: 3–25; $p = 0.496$). Tumour size was smaller for patients in groups A and B (median: 10 mm, range 1–40) compared to group C (median: 33 mm, range: 3–100; $p = 0.003$). There was a positive correlation between tumour size and interval between the last visit in all patients ($p = 0.022$).

Conclusion: Regular follow-up of OL resulted in early detection of MT. If properly selected, follow-up of OL performed by the dentist seems feasible.

KEYWORDS
early detection of cancer, oral cancer, oral epithelial dysplasia, oral leukoplakia, oral potentially malignant disorder, oral squamous cell carcinoma

1 | INTRODUCTION

Oral leukoplakia (OL) is the most common oral potentially malignant disorder (OPMD) with an estimated worldwide prevalence between 1.5% and 4.1% (Mello et al., 2018; Petti, 2003). The pooled proportion of malignant transformation (MT) of OL into oral squamous cell carcinoma (OSCC) is 9.8%, whereby the time to develop into OSCC varies greatly from patient to patient (Figure 1; Aguirre-Urizar et al., 2021; Dost et al., 2014). We have recently reported a constant annual MT rate of 4.9% in our cohort of OL patients (Evren et al., 2020). This forms the rationale for a long or even lifelong periodical follow-up. There are several independent clinical, histopathological and potential molecular features of OL that have been reported as possible predictive indicators for MT (Guan et al., 2023;

Monteiro et al., 2021; Speight et al., 2018; Wils et al., 2023). However, these risk factors are not accurately enough for predicting MT of OL in individual cases. There is a high recurrence rate after surgical excision or CO_2-laser evaporation of OL and up to now, there are no effective treatment modalities to prevent MT of OL (Lodi et al., 2016; Sundberg et al., 2019). Therefore, treated and untreated patients are in general monitored at regular intervals. The main reason for regular periodic control is the possible early detection of MT of OL or of OSCC elsewhere in the oral cavity. This is of importance since treatment of early OSCC is associated with high survival rates, limited treatment-related side effects and better quality of life outcomes (Gomez et al., 2009; Gonzalez-Moles et al., 2022; Jawert et al., 2021; Ribeiro-Rotta et al., 2022; Rusthoven et al., 2010). There are no scientific data available regarding the optimal interval between periodic follow-up visits or the added value of follow-up visits per se on early diagnosis of oral cancer. Since long-term follow-up results in an ever-increasing number of patients, these regular check-ups are time consuming for patients and healthcare professionals resulting in an increase in healthcare costs and the question is whether this time investment is justified and cost-effective. The aim of the present study was to assess whether a clear and strict regular follow-up regime in a defined cohort of patients with OL resulted in early detection of an OSCC in case of MT. We hypothesise that patients who were monitored on a regular base have smaller OSCCs compared to those who had no regular follow-up.

2 | PATIENTS AND METHODS

In this retrospective study, 222 patients with the clinical diagnosis OL were included. All patients were referred to the department of Oral and Maxillofacial Surgery/Oral Pathology at the Amsterdam University Medical Center location Vrije Universiteit Amsterdam between 1 January 1997, and 1 June 2021. They were referred by dentists, general practitioners, or medical specialists in our medical service area. In this study, the definition of OL according to the WHO was used (Warnakulasuriya et al., 2007). The data on demographics, habits and clinical characteristics were recorded during the first visit and the histopathological diagnosis of the first biopsy. Smoking and alcohol consumption were noted in a simplified manner as user, non-user (including past-user) or unknown, at time of first visit. The subsites of OL were classified as tongue, floor of mouth (FOM), alveolus and gingiva, buccal mucosa, palate and lip. The size of OL was categorised on the bases of the greatest length: <2 cm, 2–4 cm or >4 cm. Cumulative lesion size was reported in case of multiple sites. The clinical presentation of the OL was either homogeneous (predominantly white, flat, thin or wrinkled) or non-homogeneous (mixed white-and-red, including speckled, nodular, granular and verrucous). In all cases, a photograph of the lesion had been taken at patient's first visit.

As part of the diagnostic workup when the medical history and the clinical aspect suggested an etiological factor, for example, tobacco use ('smoker's lesion'); dental restoration ('contact lesion'); or mechanical irritation ('frictional lesion'), the lesion was observed for a maximum of 6–8 weeks after termination of the possible etiological factor. If the lesion had not disappeared, a definitive clinical diagnosis of OL was made. In all OL patients, a biopsy was taken at initial visit or within a few weeks after this visit. Small lesions were surgically excised and for large lesions an incisional biopsy was performed to exclude OSCC and to assess the absence or presence and grading of epithelial dysplasia. For this paper, we adhered to the original histopathological diagnosis on the biopsies of the patients, since follow-up and eventually treatment was based thereon. The biopsies were scored in the regular diagnostic workup of the Pathology Department with different pathologists as assessor. Dysplasia was recorded according to the WHO guidelines at the time of the biopsies (Barnes et al., 2005; El-Naggar et al., 2017; Pindborg et al., 1997). Patients who developed an OSCC during the first year of follow-up were excluded from the study since there may have been a micro-invasive carcinoma missed by biopsy sampling error.

With respect to follow-up, three groups of patients could be distinguished:

Group A, *follow-up hospital*: Patients had follow-up at regular intervals at the outpatient clinic conducted by a specialist Oral and Maxillofacial Surgery. In most cases, the intervals varied between 6 months and 12 months, depending on the clinical features and histopathological diagnosis of the OL. Due to missed appointments, some patients had a longer interval between their follow-up visits.

Group B, *follow-up dentist*: Patients had initially regular follow-up at the outpatient clinic. Based on the clinical features and

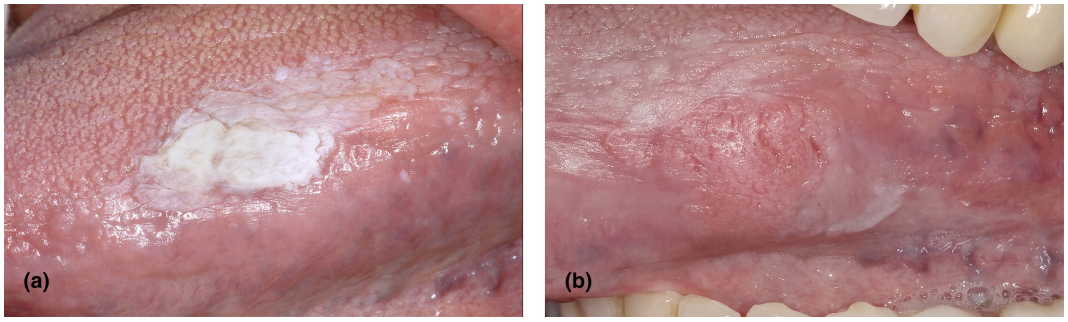

FIGURE 1 Patient with homogeneous oral leukoplakia on the left lateral border of the tongue. An incisional biopsy showed hyperkeratosis (a). Patient was monitored every 6 months. Six years after the first visit an oral squamous cell carcinoma was diagnosed (b).

histopathological diagnosis of OL, patients' request and the fact that they had regular dental check-ups, these patients were referred back to their general dentists, who were informed about the specific follow-up regime. When there was a clinical change or suspicion of MT of OL during periodic dental examination, the patient was referred to the outpatient clinic and a biopsy was taken on indication.

Group C, lost to follow-up: Patients were lost to follow-up after having a number of regular check-ups but subsequently failing to show up at either the outpatient clinic or dentist appointment, despite repeated requests. Due to the clinical suspicion of cancer, some patients who were lost to follow-up, were referred back to the hospital by dentists, general practitioners or medical specialists. Patients with a possible cancer diagnosis who were referred to other hospitals and about whom we were not informed, obviously could not be included.

Two groups of patients can be identified regarding follow-up: one group of patients (A and B) with regular follow-up and one group of patients (C) who at a certain moment were lost to follow-up.

2.1 | Ethical approval

The study protocol was approved by the Institutional Review Board of Amsterdam University Medical Center location Vrije Universiteit Amsterdam (FWA00017598). The Board decided that the Dutch Medical Research Act Involving Human Subjects (WMO) did not apply to this study and the study was registered under 2019.135. The study followed the principles of the Helsinki Declaration, the national guidelines for secondary use of human tissue of the Dutch Federation of Biomedical Scientific Societies (www.federa.org) and the General Data Protection Regulation of the European Commission.

2.2 | Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 28 for Windows (IBM Corp., Armonk, N.Y., USA) and R (programming language for statistical computing, R core team). For normally distributed data, the independent-samples *t*-test was used to assess differences in continuous variables and for other data, the Mann–Whitney *U* test was used. The Fisher's exact test was used to assess differences between dichotomous variables, and the Pearson Chi-Square test was used when there were more than two nominal categories. To test correlations, the Spearman's rank correlation coefficient was used. The results were considered statistically significant if the *p*-value was lower than 0.05.

3 | RESULTS

The total cohort of 222 consecutive patients with OL (147 females, 75 males) had a mean age at their first visit of 60 years (range 26–97; SD = 13.1) and a median follow-up period of 64 months (range: 12–300). Data on demographics, habits, clinical and histopathological characteristics, follow-up and treatment of the total group and the three distinguishable groups with regard to follow-up, are presented in Table 1.

Group A (follow-up hospital) consisted of 92 (41%) patients (61 females, 31 males) with a mean age of 60 years at first visit (range: 26–83; SD: 11.4) and a median follow-up period of 58 months (range: 12–253). The histopathological diagnosis of the first biopsy was hyperkeratosis in 50 (54%) patients and dysplasia in 42 (46%) patients.

Group B (follow-up dentist) consisted of 84 (38%) patients (57 females, 27 males) with a mean age of 57 years at first visit (range: 29–90; SD: 13) and a median follow-up period of 130 months (range: 13–300). The histopathological diagnosis of the first biopsy was hyperkeratosis in 65 (78%) patients and dysplasia in 17 (20%) patients. In two cases (2%), the histopathological diagnosis could not be assessed.

Group C (lost to follow-up) consisted of 46 (21%) patients (29 females, 17 males) with a mean age of 63 years at first visit (range: 27–97; SD: 15.7) and a median follow-up period of 70 months (range: 13–225). The histopathological diagnosis of the first biopsy was hyperkeratosis in 27 (59%) patients and dysplasia in 19 (41%) patients.

There were statistically significant differences between the groups. When compared to group A, patients in group B had smaller lesions (<2 cm: 57% vs. 30.5%; $p < 0.001$), more hyperkeratosis (78% vs. 54%; $p < 0.001$), less moderate and severe epithelial dysplasia (24% vs. 60%; $p < 0.001$), had more excisional biopsies and treatments during their follow-up at the hospital (80% vs. 59%; $p = 0.002$) and had longer follow-up (130 vs. 58 months; $p < 0.001$). Between group A and group C, only the mean age at first visit was statistically significant (60 vs. 63 years; $p = 0.011$, Independent-samples *t* test). Between group B and group C, mean age (57 vs. 63 years; $p = 0.021$, Independent-samples *t* test), length of follow-up (129 vs. 70 months; $p < 0.001$, Mann–Whitney *U* test) and presence of dysplasia (20% vs. 40%; $p = 0.012$, Fisher's exact test) were statistically significant. Between group A + B and group C, only the mean age at first visit was statistically significant (58 vs. 63 years; $p = 0.047$, Independent-samples *t* test).

There were 45 patients (20%) with MT of OL (33 females, 12 males) with a mean age at first visit of 59 years (range: 26–97; SD = 14.2) and at progression of 65 years (range: 33–99; SD = 12.9). MT occurred at a median of 59 months follow-up (range: 14–244). In Table 2, the numbers and percentages of MT of OL are depicted for the whole group and the three distinct groups A, B and C. Group A showed a higher percentage of MT (35%) compared to group B (6%), which was statistically significant ($p < 0.001$, Pearson Chi-square test). Table 3 presents patient's demographics, habits, clinical, histopathological and treatment characteristics and the clinical size of the OSCC of the total group and the, respectively, distinguishable groups: group A, group B, groups A and B combined (regular follow-up) and group C. Figure 2 illustrates the number of visits, biopsies taken, treatments and clinical tumour size of individual patients

TABLE 1 Patient, clinical, histopathological and treatment characteristics of 222 patients with oral leukoplakia.

Characteristic	Patients (%)				
Group	Total	A. Follow-up hospital	B. Follow-up dentist	*p*-value between group A and B	C. Lost to follow-up
Total (*n*)	222	92 (41)	84 (38)		46 (21)
Median follow-up in months (range)	64 (12–300)	58 (12–253)	130 (13–300)	<0.001[a]	70 (13–225)
Age (years) at first visit					
Mean (SD)	60 (13.1)	60 (11.4)	57 (13)	0.076[b]	63 (15.7)
Range (median)	26–97 (60)	26–83 (62)	29–90 (58)		27–97 (63)
Gender					
Female	147 (66)	61 (66)	57 (68)	0.477[c]	29 (63)
Male	75 (34)	31 (34)	27 (32)		17 (37)
Smoking habits					
User	98 (44)	38 (41)	36 (43)	0.512[c]	24 (52)
Non-user	101 (46)	44 (48)	40 (48)		17 (37)
Unknown	23 (10)	10 (11)	8 (9)		5 (11)
Alcohol consumption					
User	111 (50)	49 (53)	44 (52)	0.454[c]	18 (39)
Non-user	43 (19)	19 (21)	15 (18)		9 (20)
Unknown	68 (31)	24 (16)	25 (30)		19 (41)
Clinical presentation					
Homogeneous	123 (55)	52 (57)	45 (54)	0.405[c]	26 (57)
Non-homogeneous	99 (45)	40 (43)	39 (46)		20 (43)
Subsite OL					
Tongue	72 (33)	37 (40)	21 (25)	0.362[d]	14 (31)
Alveolus and gingiva	44 (20)	15 (16)	22 (26)		7 (15)
Floor of the mouth	35 (16)	9 (10)	13 (16)		13 (28)
Multiple sites	32 (14)	15 (16)	13 (16)		4 (9)
Buccal mucosa	20 (9)	10 (11)	8 (9)		2 (4)
Palate	16 (7)	5 (5)	6 (7)		5 (11)
Lip	3 (1)	1 (1)	1 (1)		1 (2)
Size					
<2 cm	95 (43)	28 (30.5)	48 (57)	<0.001[d]	19 (41)
2–4 cm	67 (30)	28 (30.5)	24 (29)		15 (33)
>4 cm	60 (27)	36 (39)	12 (14)		12 (26)
Histopathology					
Indeterminable	2 (1)	0	2 (2)	<0.001[c]	0
Hyperkeratosis	142 (64)	50 (54)	65 (78)		27 (59)
Dysplasia	78 (35)	42 (46)	17 (20)		19 (41)
Mild	36	17	13		6
Moderate	23	16	2		5
Severe	19	9	2		8
Treatment during follow-up					
Any treatment	148 (67)	54 (59)	67 (80)	0.002[c]	27 (59)
No treatment	74 (33)	39 (41)	17 (20)		19 (51)

Note: Percentages in between parentheses are summed up to 100% vertically in the columns. Unknown or indeterminable data were considered as missing and therefore excluded from statistical analyses.

[a]Mann–Whitney *U* test.

[b]Independent-samples *t* test.

[c]Fisher's exact test.

[d]Pearson's chi-square test.

TABLE 2 The number and percentage of malignant transformation for each group of patients.

	Total patients	Malignant transformation
Group A, follow-up hospital	92	32 (35%)
Group B, follow-up dentist	84	5 (6%)
Group C, lost to follow-up	46	8 (17%)
Total	222	45 (20%)

during follow-up for groups A, B and C respectively. Most OLs were located on the tongue (21 patients; 47%), non-homogeneous OL was present in 26 patients (58%) and the histopathological diagnosis of the first biopsy was hyperkeratosis in 23 (51%) and epithelial dysplasia in 22 (49%) patients. The first biopsy of OLs < 2 cm was more frequently an excisional biopsy, while OLs > 4 cm had more incisional biopsies ($p = 0.040$, Fisher's exact test). OLs < 2 cm were treated more often during follow-up than OLs > 4 cm ($p = 0.029$, Fisher's exact test). Except for four cases, all patients with dysplasia were treated at some point during the control period. Three of these four cases had mild dysplasia and one patient with severe dysplasia refused treatment. Detailed data of all 45 patients with MT of OL are given in Table S1. In all but four cases (patient: 11, 24, 38 and 45), MT occurred in the OL.

Group A (32 patients; 71%) and group B (5 patients; 11%) had a median regular follow-up period of 34 (range: 9–242) and 82 months (range: 49–120), respectively, which did not differ significantly ($p = 0.106$, Mann–Whitney *U* test). Compared to group A, in group B, significantly smaller OL lesions were found (<2 cm; $p = 0.044$, Pearson Chi-square test). Although a striking difference was observed in the number of patients with hyperkeratosis and dysplasia between group A and group B, it did not reach statistical significance ($p = 0.187$, Fisher's exact test). The median clinical tumour size in group A was 15 mm (range: 1–40 mm) and in group B 10 mm (range: 3–25 mm), which was not statistically significant different ($p = 0.496$, Mann–Whitney *U* test), which may be due to the small size of group B. Group C (8 patients; 18%) had an initial median regular follow-up period at the hospital of 25 months (range: 13–85). Compared to group A + B, group C had statistically significant more OLs located in the FOM ($p = 0.002$). The median clinical tumour size in group C was 33 mm (range: 3–100 mm), which was significantly larger than that of group A + B combined (median 10 mm; range: 1–40 mm; $p = 0.003$, Mann–Whitney *U* test). The clinical tumour size of all patients is presented in Figure 3. The clinical tumour size was 10 mm or less in 51% of the cases and between 11 and 20 mm in 38%. There was a statistically significant positive correlation between the clinical tumour size and the time of the interval between the last visit and MT ($r = 0.341$, $p = 0.022$; Figure 4). The median clinical tumour size of OLs that had any form of treatment during follow-up was 10 mm (range: 1–40 mm), which was significantly smaller compared to OLs that were not treated during follow-up (median 20 mm; range 3–100 mm; $p = 0.046$, Mann–Whitney *U* test).

4 | DISCUSSION

The annual MT rate of OL remains consistent throughout the years (Evren et al., 2020). Since there is no effective management to prevent MT of OL, patients with OL usually remain under regular periodic check-ups for many years or even lifelong at oral medicine or head and neck cancer centres with the aim of early detection of an OSCC developing from OL or elsewhere in the oral cavity (Epstein et al., 2007; Lodi et al., 2016; Mehanna et al., 2009). This is important because treatment of early OSCCs has a good prognosis, limited treatment-related side effects and better quality of life (Gomez et al., 2009; Gonzalez-Moles et al., 2022; Jawert et al., 2021; Ribeiro-Rotta et al., 2022; Rusthoven et al., 2010). Treatment of late-stage OSCC is usually extensive and expensive due to combined treatment modalities with long and repeated hospital stays, risk of complications, rehabilitation services, restorative treatments, development of early and late treatment-related side effects and major economic and social implications. The aim of the present study was to investigate whether patients with a clear and strict regular follow-up regime of a defined cohort of patients with OL resulted in early detection in case of MT. The results showed that this policy indeed resulted in early detection of OSCC arising from OL. The clinical tumour size was 10 mm or less in 51% of the cases, between 11 and 20 mm in 38% resulting in 89% of patients with tumours smaller than 20 mm, whereas most of the patients who were lost to follow-up had larger clinical tumour sizes. It is noteworthy to highlight the frequent occurrence of clinical tumour sizes measuring 10, 15 or 20 mm, which likely reflects the inherent approximation in the estimation of the tumour size. Patients in groups A and B, despite having similar numbers of OL, showed a notable difference in MT percentages, 35% and 6% respectively. Group B had compared to group A, a significant longer follow-up period, but showed a lower percentage of MT than group A. This may indicate that some other factors have contributed to the difference in MT rates and is presumably explained by differences in clinical and histopathological characteristics between the groups. It appears that a group of patients were specifically selected for periodically follow-up at the hospital outpatient clinic, including patients who did not have a dentist, and patients with regular dental check-ups who were referred back to their dentist. The latter group had other clinical and histopathological characteristics, including more OLs located on the alveolus/gingiva, smaller lesion size, more hyperkeratosis and less moderate and severe dysplasia. It is noteworthy that patients in group B underwent more excisional biopsies and more treatments during their follow-up at the hospital. A plausible explanation for this observation might be related to the nature and location of their lesions, suggesting that they had smaller, more accessible lesions, which facilitated more interventions and treatments. These differences in the features of the groups suggest that consultants at the outpatient clinic deemed the chance for MT in these patients to be low, therefore justifying their referral back to the dentists.

A recent study reported that regular follow-up at a specialised centre for patients with OPMDs, consisting mainly of patients with

TABLE 3 Patient, clinical, histopathological and treatment characteristics of 45 patients with malignant transformation of oral leukoplakia for each group and follow-up combined group versus lost to follow-up group.

Characteristic	Patients (%)					
Group	Total	A. Follow-up hospital	B. Follow-up dentist	A + B. Follow-up	C. Lost to follow-up	*p*-value between group A + B and C
Total (*n*)	45	32	5	37	8	
Median time from first visit to MT in months (range)	59 (14–244)	40 (14–244)	86 (56–131)	56 (14–244)	76 (21–125)	0.320[b]
Median regular follow-up in months (range)[a]	34 (9–242)	34 (9–242)	82 (49–120)	49 (9–242)	25 (13–85)	0.035[b]
Age (years) at first visit						
Mean (SD)	59 (14.2)	59 (13.6)	50 (12.9)	57 (13.6)	66 (15.3)	0.114[c]
Range (median)	26–97 (61)	26–82 (62)	36–66 (54)	26–82 (60)	46–97 (67)	
Age (years) at progression						
Mean (SD)	65 (12.9)	64 (11.8)	58 (14.3)	63 (12.2)	73 (14.3)	0.061[c]
Range (median)	33–99 (66)	33–86 (66)	41–77 (59)	33–86 (65)	53–99 (72)	
Gender						
Female	33 (73)	26 (81)	2 (40)	28 (76)	5 (63)	0.359[d]
Male	12 (27)	6 (19)	3 (60)	9 (24)	3 (37)	
Smoking habits						
User	18 (40)	13 (41)	0	19 (51)	3 (37)	0.237[d]
Non-user	22 (49)	14 (44)	5 (100)	5 (14)	0	
Unknown	5 (11)	5 (15)	0	13 (35)	5 (63)	
Alcohol consumption						
User	22 (49)	15 (47)	2 (40)	17 (46)	5 (63)	0.435[d]
Non-user	6 (13)	4 (12)	2 (40)	6 (16)	0	
Unknown	17 (38)	13 (41)	1 (20)	14 (38)	3 (37)	
Clinical presentation						
Homogeneous	19 (42)	13 (41)	3 (60)	16 (43)	3 (37)	0.544[d]
Non-homogeneous	26 (58)	19 (59)	2 (40)	21 (57)	5 (63)	
Subsite OL						
Tongue	21 (47)	17 (53)	3 (60)	20 (54)	1 (13)	0.002[e]
Floor of the mouth	5 (11)	1 (3)	1 (20)	2 (5)	3 (37)	
Lip	2 (4)	2 (6)	0	2 (5)	0	
Palate	2 (4)	0	0	0	2 (25)	
Buccal mucosa	5 (11)	4 (13)	1 (20)	5 (14)	0	
Multiple sites	10 (22)	8 (25)	0	8 (22)	2 (25)	

TABLE 3 (Continued)

Characteristic	Patients (%)					*p*-value between group A + B and C
Group	Total	A. Follow-up hospital	B. Follow-up dentist	A + B. Follow-up	C. Lost to follow-up	
Size						
<2 cm	17 (38)	8 (25)	4 (80)	12 (32)	5 (63)	0.139[d]
2–4 cm	11 (24)	11 (34)	0	11 (30)	0	
>4 cm	17 (38)	13 (41)	1 (20)	14 (38)	3 (37)	
Histopathology						
Hyperkeratosis	23 (51)	15 (47)	4 (80)	19 (51)	4 (50)	0.624[d]
Dysplasia	22 (49)	17 (53)	1 (20)	18 (49)	4 (50)	
Mild	7	6	1	7	0	
Moderate	8	6	0	6	2	
Severe	7	5	0	5	2	
Any treatment during follow-up						
Treatment	33 (73)	26 (81)	3 (60)	29 (78)	4 (50)	0.116[d]
No treatment	12 (27)	6 (19)	2 (40)	8 (22)	4 (50)	
Clinical tumour size in mm						
Median (range)	15 (1–100)	15 (1–40)	10 (3–25)	10 (1–40)	33 (3–100)	0.003[b]

Note: Percentages in between parentheses are summed up to 100% vertically in the columns. Unknown data were considered as missing and therefore excluded from statistical analyses.

[a]The regular follow-up period was calculated by subtracting the period between the last check-up and MT from the total follow-up period.

[b]Mann–Whitney *U* test.

[c]Independent-samples *t* test.

[d]Fisher's exact test.

[e]Pearson's chi-square test.

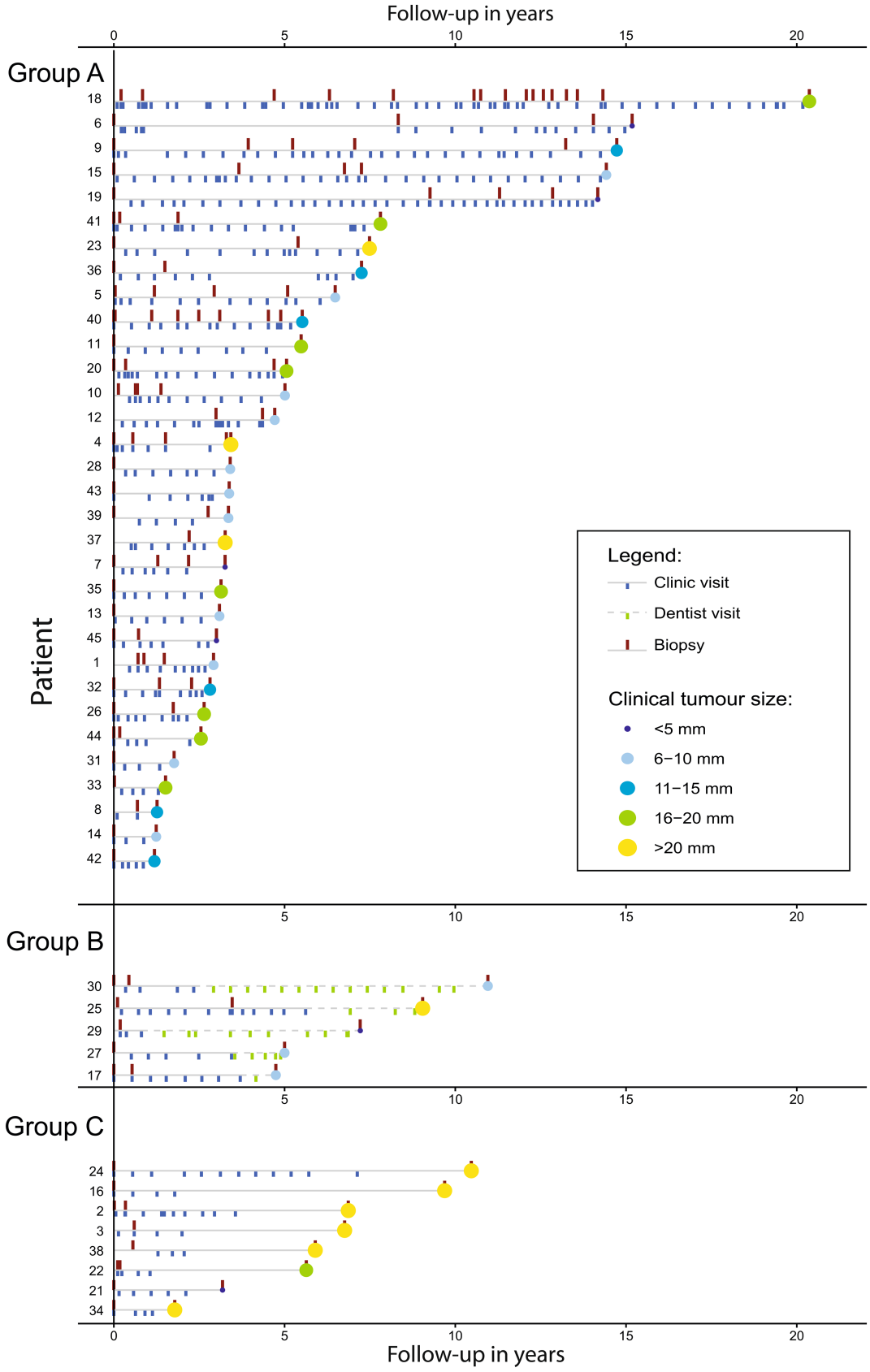

FIGURE 2 Illustration of the follow-up of each individual patient with malignant transformation of oral leukoplakia subdivided in three groups. Marks represent visits at the outpatient clinic (blue) and dentist (green) respectively. The red mark represents biopsies taken. The clinical tumour size is depicted in categories as shown in the legend.

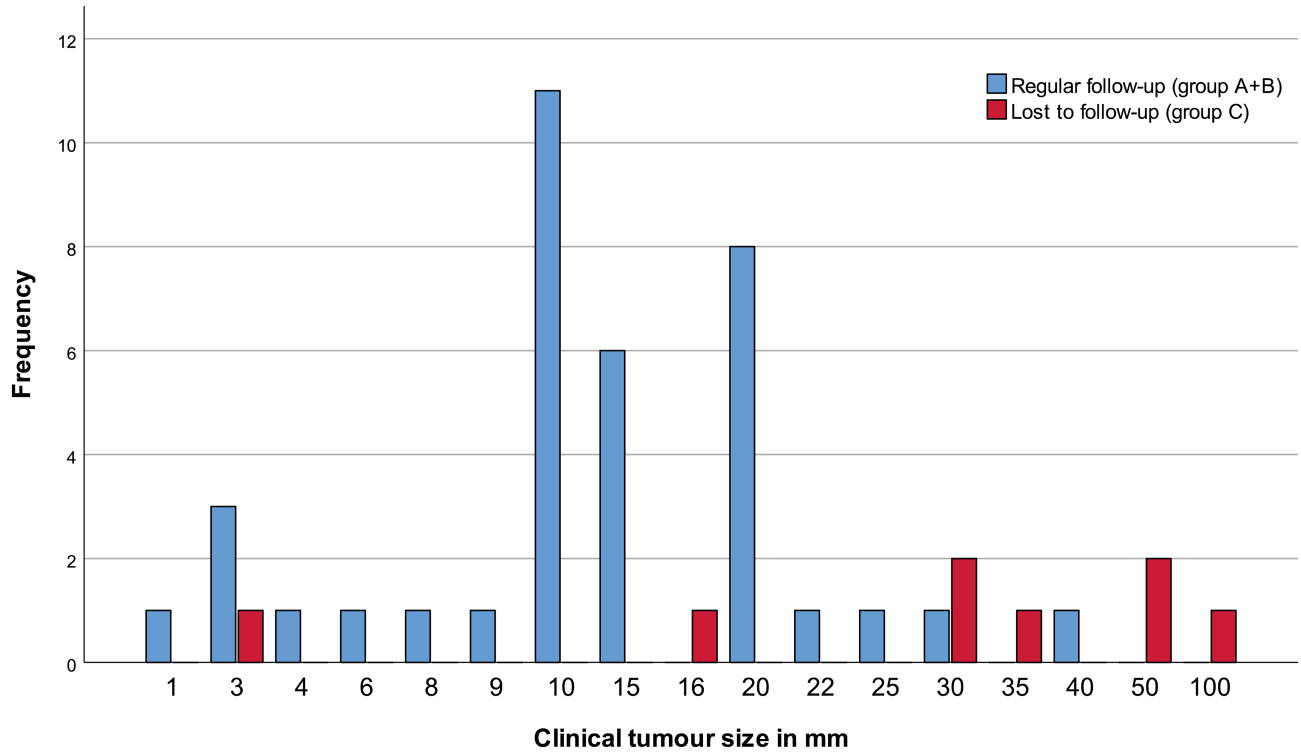

FIGURE 3 Histogram of the clinical tumour sizes in mm in group A+B with regular follow-up and group C lost to follow-up. Clinical tumour sizes in group A+B were smaller (median 10 mm; range: 1–40) than in group C (median 33 mm; range: 3–100; $p = 0.003$, Mann–Whitney U test).

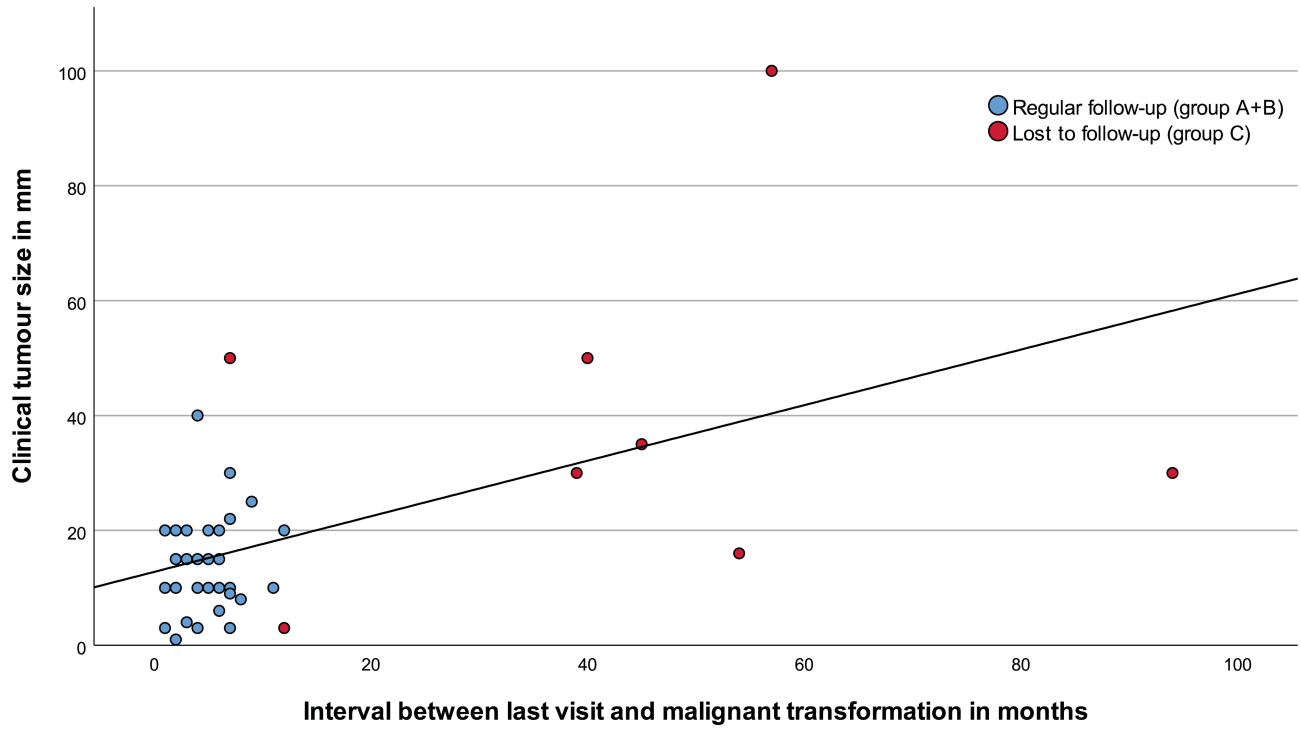

FIGURE 4 Scatter plot of the time of the interval between the last visit and malignant transformation in months (x-axis) and clinical tumour size in mm (y-axis). There was a statistically significant positive correlation between these two variables ($r = 0.341$, $p = 0.022$, Spearman's rank correlation coefficient).

OL, led to earlier detection of OSCC compared to a group of patients that were referred back to their general dentists. Although dentists were instructed on the follow-up strategy, these referred patients presented with notably larger tumour sizes (Jawert et al., 2021). This is in contrast with our finding where there was no significant difference in clinical tumour size between patients that had their

follow-up at the hospital (group A) or by their dentists (group B). This discrepancy with the aforementioned paper could possibly be explained by the fact that the authors included various OPMDs, the lack of detailed clinicopathological data of the OMPDs and whether or not these may have played a role in the decision to have the follow-up carried out by the clinician or the dentist.

Long-term follow-up of OL patients is recommended and during these follow-up visits, patients are informed about the purpose of the periodic examinations, the importance of ceasing any potential risk factor and the likelihood that cancer may occur in the OL and that early detection is important. They are also educated on the clinical signs and symptoms that may indicate the presence of an OSCC. Educating and raising awareness among patients may help diagnose OSCCs at an early stage. In this study, seven patients (22%) in group A presented earlier than their latest scheduled check-up due to clinical symptoms, potentially reflecting the heightened awareness promoted by the regular follow-up. Patients who were treated for their OL, presented with smaller clinical tumour sizes, while not preventing MT, it may made them more careful and attentive towards changes in symptoms, consequently resulting in earlier detection of OSCC. Another contributing factor to the smaller size of OSCCs in treated OLs could be due to the difference in policies whereby small OLs (<2 cm) were treated more frequently during follow-up than large OLs (>4 cm). Patients who were eventually lost to follow-up (group C) had significantly fewer follow-ups compared to groups A and B and although these patients also had been informed during their visits about the potential chance of MT of OL, they presented with larger tumours. In general, most oral cancers are diagnosed at the time when symptoms occur and patients find it difficult to observe and assess changes in the oral cavity (van der Waal et al., 2011). The greatest delay in the diagnosis of OSCC is often attributable to the patient since they do not recognise the severity of symptoms and complaints or do not pay attention to them (Panzarella et al., 2014; Peacock et al., 2008). It appears that this also holds true for patients in group C, even though they have been informed about the chance of MT of OL.

Regular periodic follow-up at the hospital is not only time-consuming for patients and their relatives, since not infrequently the patient must be assisted by a family member, but also for the doctor, nurse and administrative staff at the hospital, creating a heavy burden on the healthcare system. The WHO also indicates that healthcare workforce is under pressure due to a high percentage of staff nearing retirement age in the next decade, with inadequate recruitment and retention exacerbating the issue (WHO, 2022). Furthermore, healthcare costs in Europe are rising and are expected to increase by 0.8% annually under the current circumstances (Goryakin et al., 2020). The question about the need for long-term or even lifelong regular follow-up of patients with OL to take place at the outpatient clinic is therefore pertinent.

When patients visit their dentists for regular check-up, the dentist has the opportunity to carry out the periodic control of OL. Our data suggest that dentists appear to be able to adequately evaluate changes in the clinical aspect of OL and, if changes have occurred, subsequently refer the patient for any additional diagnostic procedure. Although it is certain that some patients might have been referred without evidence of MT found upon additional examination, it is clear that a capable, dedicated and interested dentist can properly fulfil the controlling and detecting role. However, it is not merely a matter if dentists are willing to assume this responsibility, but also whether they possess the necessary skills and knowledge, and whether this role is suitable or manageable in their practice. A lack of understanding and awareness of the clinical symptoms and aspects of OSCC among general dental practitioners could lead to inadequate recognition of OSCCs at an early stage. Only 25% of dentists find themselves sufficiently trained to provide oral cancer examinations and 41% examines their patients for oral cancer (Horowitz et al., 2000). The incidence of OSCC screening among healthcare providers in general, including dentists, is low (Coppola et al., 2021). For dentists, this could be related to insufficient knowledge on early cancer detection (Yellowitz et al., 2000). A possible solution could involve enhancing attention and awareness, alongside offering further training to general dental practitioners, so that they are better trained in performing a full oral examination and adequate follow-up of OL. Given the incidence of OL, it is not realistic that every dentist should be able to perform regular follow-up of OL. In recent years, there has been an increasing trend towards dental group practices, and within these settings, it is more likely that there are dentists who have differentiated or developed a keen interest in oral medicine (Cole et al., 2015; Guay et al., 2012). If trained and dedicated dentists are willing and amendable, they could manage the follow-up of patients with OL and refer the patients again in case of clinical changes. In line with our prior characterisations of patients with OL with a low risk of MT (Wils et al., 2020), the current study suggests that patients with small OLs, located on the gingiva/alveolus or tongue, and a histopathological diagnosis of hyperkeratosis or mild dysplasia might be suitable for regular follow-up by their dentist. Such an approach could be sufficiently predictive to allow for meaningful stratification of individual cases. This could substantially reduce the burden on the healthcare system considering that the group with only hyperkeratosis represented 64% of the current study population. In large series, the histopathological diagnosis of hyperkeratosis of OL varies from 41% to 66%, indicating the potential impact of this approach (Holmstrup et al., 2006; Lee et al., 2006; Woo et al., 2014). This is of clinical importance since hyperkeratosis is not an indicator of possible MT and may thus result in a policy that patients with the histopathological diagnosis of hyperkeratosis will not have regular follow-up. A recent study calls for a reconsideration of the molecular mechanisms that underlie the progression from hyperkeratosis to carcinoma, thereby emphasising the critical need to identify and manage OLs even in the absence of epithelial dysplasia (Stojanov & Woo, 2022).

In recent years, non-invasive diagnostic techniques, such as tissue fluorescence, have emerged as promising modalities (Walsh et al., 2021). However, their implantation in the clinic demands thorough evaluation. The intricate nature of benign conditions, such as inflammation, that mimic OPMDs could lead to

false-positive outcomes, making diagnosis challenging. Therefore, the imperative for specialised expertise in the interpretation of the results accentuates the issues with their clinical implication (Chhabra et al., 2015).

A limitation of the present study is its retrospective nature and that it relied on medical records, not all of those standardised for all data, which can result in information bias and may affect the internal validity. The study was conducted in a single specialised centre, which limits the external validity of the study findings. We realise that there is a chance that some white lesions who were diagnosed as OL were in fact frictional or contact lesions. Unfortunately, this cannot be entirely avoided. However, given our strict inclusion criteria, the number of possible misdiagnosed OLs is probably limited and thus will hardly influence the MT rate. There were small sample sizes of patients with MT who had their follow-up continued at the dentist or were lost to follow-up. Moreover, it is possible that some patients in the latter group may have had MT and were referred to another hospital. This reduces the statistical power of the study and increases the risk of type II errors.

In conclusion, the current study showed that regular follow-up of patients with OL resulted in early detection of OSCC in case of MT, reflected by small tumour sizes. This indicates the importance of regular long-term or even lifelong follow-up of OL. However, whether the follow-up should be performed in specialised centres can be questioned, since it poses a significant burden on both patients and the healthcare system. In the majority of cases, follow-up of OL can be reliably performed during regular dental check-up by dedicated and, if necessary, additionally educated dentists using the same follow-up protocol. A predictable and reliable risk profile could help to determine which patients should have follow-up in a specialised centre and who have their follow-up by their dentist.

AUTHOR CONTRIBUTIONS

Ilkay Evren: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Ahmad M. Najim:** Data curation; investigation; writing – review and editing. **Jos B. Poell:** Data curation; formal analysis; methodology; visualization; writing – review and editing. **Elisabeth R. Brouns:** Data curation; investigation; writing – review and editing. **Leon J. Wils:** Data curation; investigation; writing – review and editing. **Laura A. N. Peferoen:** Investigation; writing – review and editing. **Ruud H. Brakenhoff:** Methodology; supervision; writing – review and editing. **Elisabeth Bloemena:** Investigation; methodology; supervision; writing – review and editing. **Erik H. van der Meij:** Investigation; supervision; writing – review and editing. **Jan G. A. M. de Visscher:** Conceptualization; investigation; methodology; supervision; project administration; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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