Title:

The clinical determinants of malignant transformation in oral epithelial dysplasia

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Abstract

Background: Wile the size and clinical appearance are known risk factors for malignant transformation of potentially malignant oral lesions, the site, grade of dysplasia and exposure to environmental carcinogens remains controversial. We aim to report the clinical determinants of malignant progression in a series of patients with histologically graded oral epithelial dysplasia (OED).

Methods: We recruited patients with a histopathological diagnosis of OED to a longitudinal observational cohort study in a tertiary oral dysplasia clinic. Clinical, histopathological and risk factor data were recorded at baseline. One of three clinical endpoints were determined: malignant transformation, progression of dysplasia grade, remission / stable dysplasia grade.

Results: Ninety-one patients meeting the criteria gave consent for inclusion to the cohort, with outcomes reported after a median follow up of 48 months. An estimated 22% (SE 6%) of patients underwent malignant transformation within 5 years, with significant predictors being: non-smoking status (χ^2=15.1 p=0.001), site (χ^2=15.3 p=0.002), non-homogeneous appearance (χ^2=8.2 p=0.004), size of lesion $\geq$200mm^2 (χ^2=4.7, p=0.03) and, of borderline significance, high grade (χ^2=5.8 p=0.06). Gender, age, number of lesions and alcohol history did not predict for malignant transformation.

Conclusion: Although a number of these clinical determinants have previously been associated with higher malignant transformation in OED, the high risk nature of lesions in non-smokers is of particular note and requires a greater emphasis and recognition amongst clinicians dealing with OED. It suggests that those non-smokers with OED have an inherited

or acquired predisposition and should be treated more aggressively; these should form the focus for further investigation.

Introduction

The clinical significance of oral epithelial dysplasia(OED) lies in its association with malignant transformation into oral squamous cell carcinoma(OSCC)[1]. OED can present clinically as leukoplakia: homogenous (flat, thin, uniform white) and non-homogenous (white and red/erythroleukoplakia, speckled or nodular, verrucous leukoplakia)[2], or erythroplakia[3]. OED can only be diagnosed histologically and, although presents as a spectrum of epithelial change rather than distinct categories, the WHO 2005[4] grades as mild, moderate, severe and carcinoma-in-situ. The risk of malignant transformation has been reported to be between 6.6-36.4%, although a recent meta-analysis found the rate 12.1%[5-9]. Risk factors associated with increased malignant transformation include: female gender[10], longer duration of lesion[7;11], idiopathic leukoplakia (i.e. non-smokers)[7;10], subsite of tongue and/or floor of mouth[12-14], size $\geq$200mm^2 [15;16], non-homogenous apperance[7;15], higher grade of dysplasia[6;10;17], verrucous subtype[5;7;18;19] and the presence of multiple lesions[20]. Surgical excision has been the preferred modality of treatment in the management of OED[21], despite the lack of randomized controlled trial evidence[22] and recurrence rates of up to 35% have been reported[11]. Lesions that had not been excised demonstrated a higher rate of malignant transformation compared with those that were excised[6]. Most of the reported literature have presented outcome data on oral leukoplakia/premalignant lesions, with only a few reporting clinical outcomes of OED[5;8;17]. The purpose of this study was to evaluate the clinical factors that determined the risk of malignant transformation of OED into OSCC in a tertiary Regional Oral Dysplasia Clinic.

Patients and methods

Inclusion criteria: Patients who attended a tertiary oral dysplasia clinic with lesions clinically suspicious of OED were prospectively recruited into a clinical and molecular biomarker study since September 1999 and their demographic and pathology details were entered into a computerised database. Ethical approval for this study was given by Sefton REC (now North West – Liverpool Central; reference number: EC 47.01). Consent was obtained for retrospective and prospective analysis of tissue samples and clinical records. Inclusion was based on an initial biopsy and histological diagnosis of OED. Reporting was conducted by two oral pathologists (JAW/AT) throughout the cohort. Patients with synchronous oral squamous cell carcinoma (OSCC) were excluded.

Data collection: The following baseline data were recorded: demographic details (age, gender), smoking and alcohol history, site, clinical appearance (homogenous or non-homogenous), approximate size (measured as total surface area from clinical photographs, as documented in medical records or measurement of specimen when lesion was surgically excised), number of lesions (single or multiple), histopathological diagnosis of initial biopsy, and initial treatment (clinical observation or surgical excision) . Longitudinal follow-up data collected included the total number of biopsies and surgical excisions carried out, number of visits to the dysplasia clinic, length and status of follow-up at most recent review: (under follow-up, lost to follow-up or discharged). Histological endpoint, as defined by analysis of subsequent biopsies, were categorised as: i) remission or stable grade; ii) progression of dysplasia grade; and iii) malignant transformation.

Statistical method: Statistical analysis was carried out using the SPSS (Statistical Package for the Social Sciences) software, IBM Corporation. Kaplan-Meier methods were used to

estimate the percentage of patients who underwent malignant transformation of OED after two and five years, and the log-rank test was used to compare transformation survival curves. Cox regression methods were used to investigate the main independent predictors of survival. Hazard ratios (HR) with 95% confidence interval (95% CI) and p values were reported ($p < 0.05$ was considered statistically significant).

Results

One hundered and forty-five patients were identified from the database of consented patients. The medical records of 25 patients were not retrievable, 17 patients did not have a diagnosis of OED, for example proliferative verrucous leukoplakia or candida hyperplasia. Twelve patients with OED were excluded because the biopsy also contained OSCC. Therefore 91 eligible patients with biopsy confirmed OED were included for this analysis. The first clinic appointments for these patients were between 11 May 1984 and 16 March 2011.

The baseline information of all patients included in the study is presented in Table 1. There was a significant relationship overall between site of OED and smoking history ($p<0.01$). Most notably, 80% (12/15) of lesions sited in the lateral tongue were in the never smoked/<5 pack years group, whereas this group accounted for only 8% (3/40) of floor of mouth lesions.

At the most recent review, 23(25%) of the patients had undergone malignant transformation, 5(5%) had progressed to a more severe grade of dysplasia and 63(69%) were in remission (stable/resolved). Adjusting for difference in length of follow-up, the Kaplan-Meier estimate for the transformation rate at 2 years was 12% (SE 4%) and at 5 years was 22% (SE 5%).

Patient factors were analysed with respect to malignant transformation rate of OED by univariate Kaplan-Meier analyses to compare the transformation curves and estimate the percentage of patients who had malignant transformation after two and five years (Table 2).

The strongest univariate predictors were smoking status, appearance and sub-site, then size of lesion and severity of dysplasia (Figures 1-5).

Patient factors were used in stepwise multivariable Cox regression modelling. The first predictor into the regression was smoking status (at p=0.002), and then clinical appearance (p=0.046) for its extra independent contribution to the model (extra X^2=4.0)(Table 3).

Kaplan-Meier estimates for smoking status stratified by appearance were then determined (Table 4). When smoking status was excluded, then only site was selected in the regression modelling (p=0.01), with clinical appearance borderline for independent entry at p=0.07 in addition to site. A log-rank test comparing the malignant transformation Kaplan-Meier curves of severe dysplasia (high-risk) with mild and moderate dysplasia combined (low-risk) (Figure 4) was of borderline significance (p=0.05) and Cox regression gave a hazard ratio of 2.2 (95% CI 0.9-5.1; p=0.08)).

The method of treatment after initial assessment (excise vs review) did not influence malignant transformation rate, no doubt influenced by prescription bias (Log rank χ^2=1.3 p=0.25, 5 year transformation: excise 28(12)% , review 21(6)%.

Data related to the number of incisional biopsies and surgical excisions, number of clinic attendances and follow-up duration is shown in Table 6. In the malignant transformation group, the median time from malignant transformation from first clinic appointment was 48 months (IQR 10-84). The follow-up status of patients at the time of reporting was: 42(46%) under follow-up, 37(41%) lost to follow-up and 12(13%) discharged from the clinic, mostly to review in primary care.

Discussion

In this study, we report relatively high malignant transformation rate of 22% at 5 years amongst patients diagnosed with OED undergoing long-term follow-up. Factors such as non-smoking, lateral tongue site and non-homogenous appearance were all associated with a 5-year malignant transformation rate of around 40% or greater, although the former two were inter-dependent factors. Non-smokers were 7.1 times more likely to undergo malignant transformation compared to heavy smokers. Malignant transformation occurred after a median of 48 months following diagnosis of dysplasia.

In comparison with 7-27% reported in several hospital based cohorts[5;8;17], the overall malignant transformation rate in this study falls at the high end of the spectrum. One reason for this may be recruitment bias due to the tertiary nature of the Regional Dysplasia Clinic, although this setting is common to most other studies. Variation in the length of clinical follow up may also account for some of the differences in reported transformation rates. Most publications in the literature use a clinical diagnosis of oral leukoplakia rather than a histological diagnosis of OED[7;10;15;23]. Our tight inclusion criteria of biopsy confirmed OED is likely to have contributed to the high rates observed. The advantages of our strict inclusion protocol with prolonged follow-up are self-evident, but this has resulted in a relatively modest total number of patients studied and resultant wide confidence intervals in the estimates of transformation reported.

The particularly high rate of transformation in non-smokers is noteworthy and we speculate that underlying endogenous factors may be responsible. Non-homogenous lesions transformed more often, consistent with several previous reports[7;10;15;16], one of which found this to be the only factor predictive of malignant transformation[8]. The non-

homogenous appearance of the lesion, amongst other patient factors, has raised clinical suspicion and resulted in the prescription of a more aggressive approach to treatment by surgical excision (Table 5).

In order to reduce inter-observer variability of histolopathological grade, a binary system[24] has recently been suggested constituting low-risk (mild & moderate dysplasia) and high-risk (severe dysplasia and carcinoma-in-situ). Our finding that mild and moderate dysplasia grouped closely together as low risk lesions (figure 4) supports the clinical validity this binary grading.

The lateral tongue Figure 6) and floor of mouth Figure 7) have both previously been associated with an increased risk of malignant transformation[5;11]. In our study, lesions on the lateral tongue had the highest propensity for malignant transformation (Kaplan-Meier 5 year estimate 53%) whilst the commonest site with OED was the FOM, making up 44% (40/91) of lesions, with malignant transformation estimated as 8% at 5 years. This unexpectedly large difference highlights the need for close supervision in lateral tongue lesions. It would be interesting to explore whether the low rates of smoking in lateral tongue lesions we report are reproduced in other series. The size of the lesion, although not independently predictive of malignant transformation, was statistically significant when the transformation rates were compared, and larger lesions ($\geq$200mm^2) appear to have a higher propensity for malignant transformation supported by findings of earlier reports[15;16]. The median time to malignant transformation of 48 months in our cohort supports the need for long-term clinical follow-up, with the longest case taking 297 months for malignant transformation, not dissimilar to results of a recent meta-analysis[6]. Although 41% (37/91) of patients were lost to follow-up at the time of reporting, within this subgroup of patients: 26% (24/91) had been followed-up for at least 2 years and 15% (14/91) had in excess of 5-

years follow-up. Thus conclusions drawn from the clinical outcomes of this study have not been compromised by what, on the surface, appeared to be a high rate of poor follow-up.

The clinical determinants of malignant transformation reported in this study will hopefully facilitate decision-making in respect of interventions that can be offered to patients. Our observations also highlight the potential for differing mechanisms of carcinogenic route between smoking-associated and non-smoking associated OED. The prolonged follow-up and multiple interventions in a multi-disciplinary clinic utilise significant resources, however when viewed in the context of 40-50% transformation rates seen in some groups, this is clinically justifiable and in the best interests of these patients. Discharge of those in lower risk cohorts for ongoing review in primary care may also be feasible with adequate safeguards. In the future, risk stratification of patients is still likely to be dependent on clinical and histological features, but may also be influenced by predictive biomarkers reflecting the known genetic[25,26] and epigenetic [27,28] determinants of malignant progression.

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Table 1 Baseline information of 91 patients at initial presentation

		Number of patients (%)
Gender	Male	49(54)
	Female	42(46)
Age(at first appointment)	<50.0	26(29)
	50.0-59.9	37(41)
	≥60.0	28(31)
Site of OED	Floor of mouth (FOM)	40(44)
	Buccal mucosa	16(18)
	Lateral tongue	15(16)
	Others:	20(22)
	Soft palate	7
	Mandibular alveolar/gingival	4
	Maxillary alveolar/ gingival	1
	Ventral tongue	5
	Dorsum tongue	1
	Hard palate	1
	Tonsillar	1
Size of OED (largest in cases with multiple lesions)*	< 200mm^2	37(42)
	≥ 200 mm^2	52(58)
Diagnosis (first biopsy)	Mild dysplasia	40 (44)
	Moderate dysplasia	31 (34)
	Sever dysplasia	20 (22)
Number of lesions	Single	70(77)
	Multiple	21(23)
Clinical appearance	Homogenous white	65(71)
	Others:	26(29)
	Erythroleukoplakia	18
	Erosive (red patch)	6

	Ulcer	2
Smoking history	Never or <5 pack yrs	20(22)
	5-20 pack yrs	29(32)
	>20 pack yrs	42(46)
Alcohol consumption	Teetotal or <5 units per week	42(46)
	5-20 units per week	27(30)
	>20 units per week	22(24)
Previous OSCC	Yes	5(5)
	No	86(95)

* not known for 2 patients therefore n=89(100%) for this parameter

Table 2. Two and five year Kaplan-Meier transformation rates %(SE) and Cox regression estimates of Hazard ratio

			Transformation rate estimate			HR** with 95% CI
		Patients	2yr	5yr	Log rank test	
	TOTAL	91	10 (3)	22 (6)		
Gender	Male	49	8 (5)	18 (8)	χ^2=0.3	-
	Female	42	12 (5)	26 (8)	p=0.57	1.3 (0.5-2.9)
Age	<50	26	4 (4)	16 (9)	χ^2=3.3 p=0.19	-
	50-59	37	12 (7)	18 (8)		1.0 (0.3-3.0)
	60+	28	15 (7)	33 (11)		2.1 (0.7-5.7)
Site	Floor of Mouth	40	3 (3)	8 (5)		-
	Buccal	16	6 (6)	29 (15)	χ^2=15.3	1.9 (0.6-6.2)
	Lateral Tongue	15	29 (12)	53 (16)	p=0.002	4.9 (1.7-13.7)
	Other	20	11 (8)	18 (10)		0.9 (0.2-3.5)
Size of lesion*	<200 mm^2	37	8 (5)	13 (7)	χ^2=4.7	-
	200+ mm^2	52	12 (5)	28 (8)	p=0.03	3.0 (1.0-8.7)
Diagnosis (first biopsy)	Mild	40	3 (3)	16 (8)	χ^2=5.8	-
	Moderate	31	5 (5)	24 (11)	p=0.06	2.2 (0.8-6.1)
	Severe	20	33 (11)	33 (11)		3.2 (1.1-9.2)
Number of lesions	Multiple	21	15 (8)	24 (11)	χ^2=0.5 p=0.49	1.3 (0.6-3.3)
	Single	70	9 (4)	22 (6)		-
Appearance	Homogenous white	65	3 (2)	15 (6)	χ^2=8.2 p=0.004	-
	Other	26	26 (9)	38 (11)		3.0 (1.3-6.8)
Smoking	Never or <5 pack yrs	20	27 (10)	43 (13)	χ^2=15.1	7.1 (2.2-22.6)
	5-20 pack yrs	29	7 (5)	30 (11)	p=0.001	3.23 (1.0-10.5)
	>20 pack yrs	42	4 (4)	4 (4)		-
Alcohol	Teetotal or <5units/week	42	10 (5)	25 (8)		-
	5-20 units per week	27	14 (8)	22 (10)	χ2=0.5 p=0.76	0.9 (0.3-2.4)
	>20 units per week	22	5 (5)	16 (11)		0.7 (0.2-2.1)

*NK for 2

** Hazard ratio (relative risk of death) with 95% confidence interval

Table 3. Final model of independent predictors for the 91 patients using multi-variable Cox regression

	Hazard ratio (relative risk of death)	95% CI of Hazard ratio
Smoking status:		
>20 pack years	Relative to '>20 pack years'	
5-20 pack years	2.8	0.8 – 9.1
Never or <5 pack years	5.9	1.8 -19.2
Appearance:		
Homogenous white	Relative to 'Homogenous white'	
Other	2.3	1.0 – 5.4

Table 4. Kaplan-Meier analyses with regard to smoking status and lesion appearance. 2 and 5-year Kaplan-Meier transformation rates (SE)

			Transformation rate estimate		
		Patients	2yr	5yr	Log rank test (within strata)
Appearance : Homogenous white					
Smoking	Never or <5pack yrs	12	9 (9)	38 (18)	χ^2=7.0
	5-20 pack yrs	19	5 (5)	22 (12)	p=0.03
	>20 pack yrs	34	0 (-)	0 (-)	
Appearance: Other					
Smoking	Never or <5pack yrs	8	53 (19)	53 (19)	χ^2=5.1
	5-20 pack yrs	10	10 (10)	38 (18)	p=0.08
	>20 pack yrs	8	20 (18)	20 (18)	

Log-rank test of equality of malignant transformation distributions for the different levels of smoking, adjusted for appearance: X^2=11.6, p=0.001.

Log-rank test of equality of malignant transformation distributions for the different levels of appearance, adjusted for smoking status: X^2=4.8, p=0.03.

Table 5. Total number of biopsies (and surgical excision), number of clinic attendances and follow-up duration for 91 patients

Group	Total number of biopsies (and surgical excision) Median (IQR)	Number of clinic attendances Median (IQR)	Follow-up period (months) Median (IQR)
Malignant transformers (n=23)	4(3-6)	15(10-32)	82(33-121)
Remission and progression (n=68)	1(1-2)	9(5-18)	42(15-78)
All patients (n=91)	2(1-3)	11(5-19)	48(18-96)

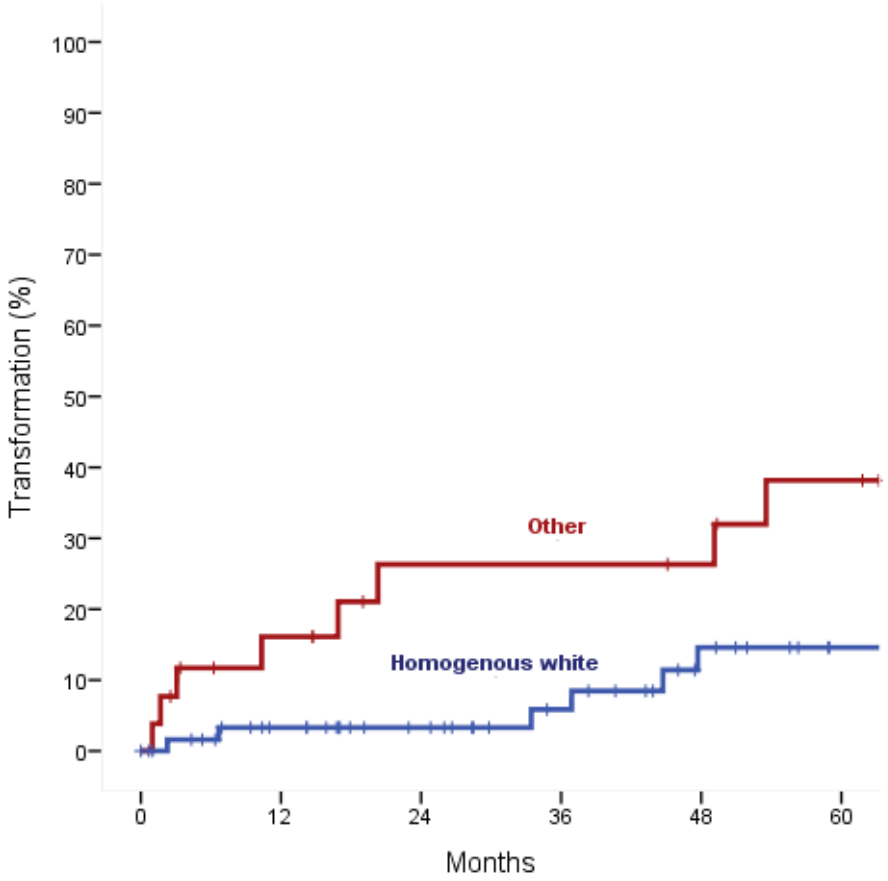

Figure 1 Kaplan-Meier curves for malignant transformation rates: appearance of lesion

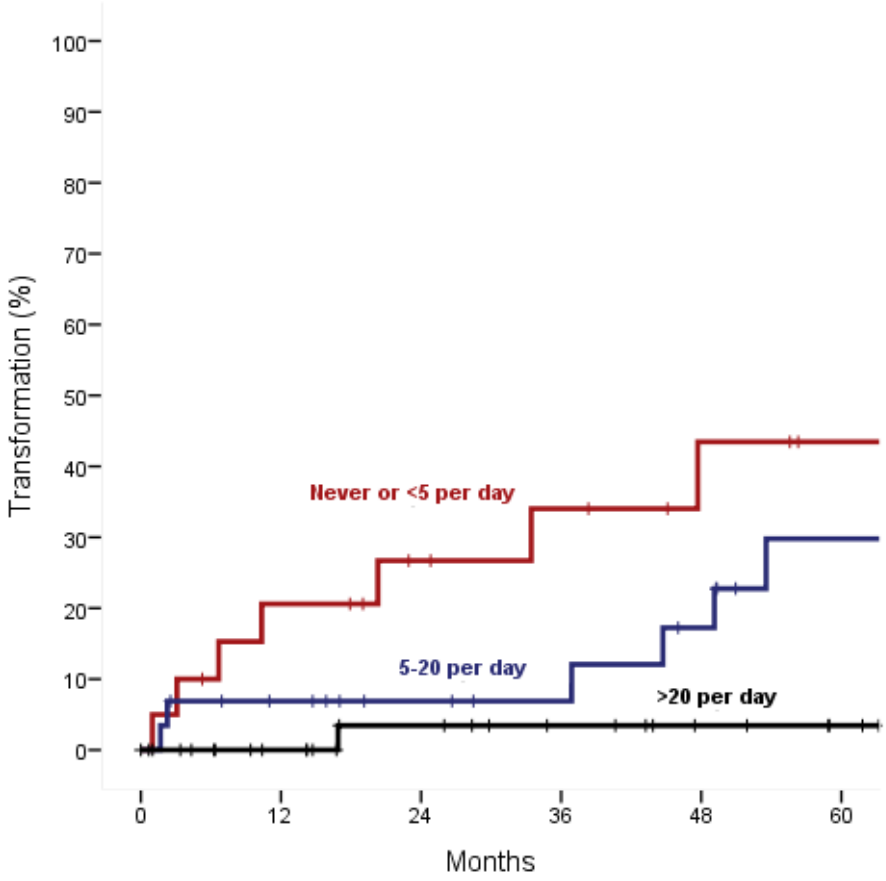

Figure 2 Kaplan-Meier curves for malignant transformation rates: smoking history

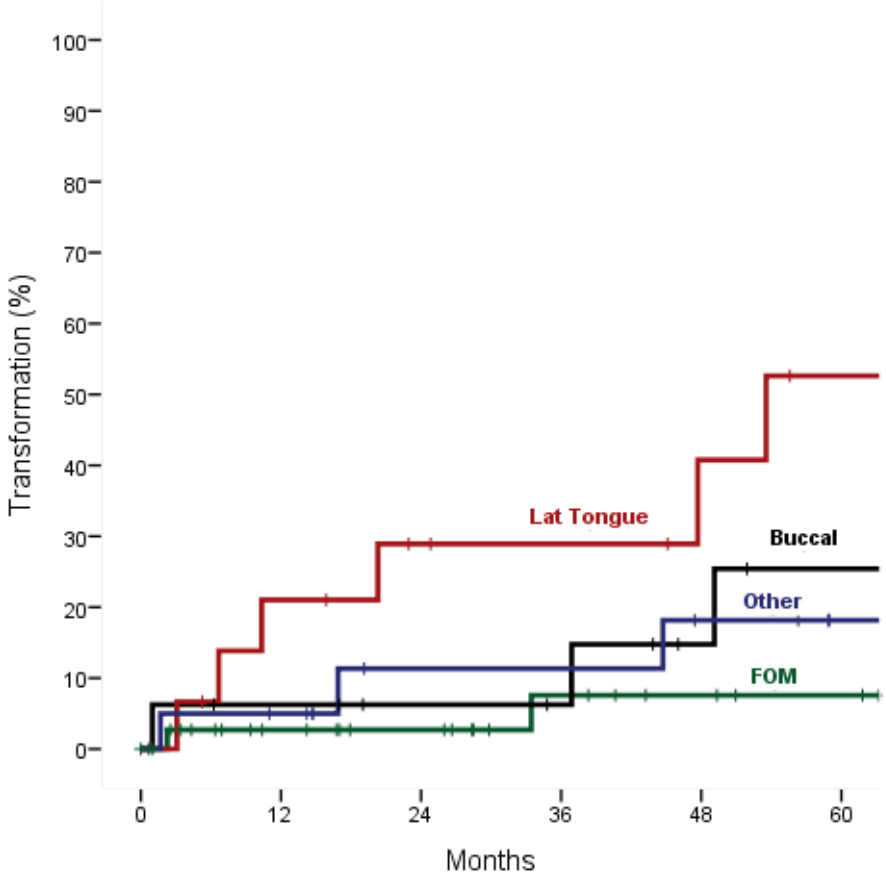

Figure 3 Kaplan-Meier curves for malignant transformation rates: site of lesion

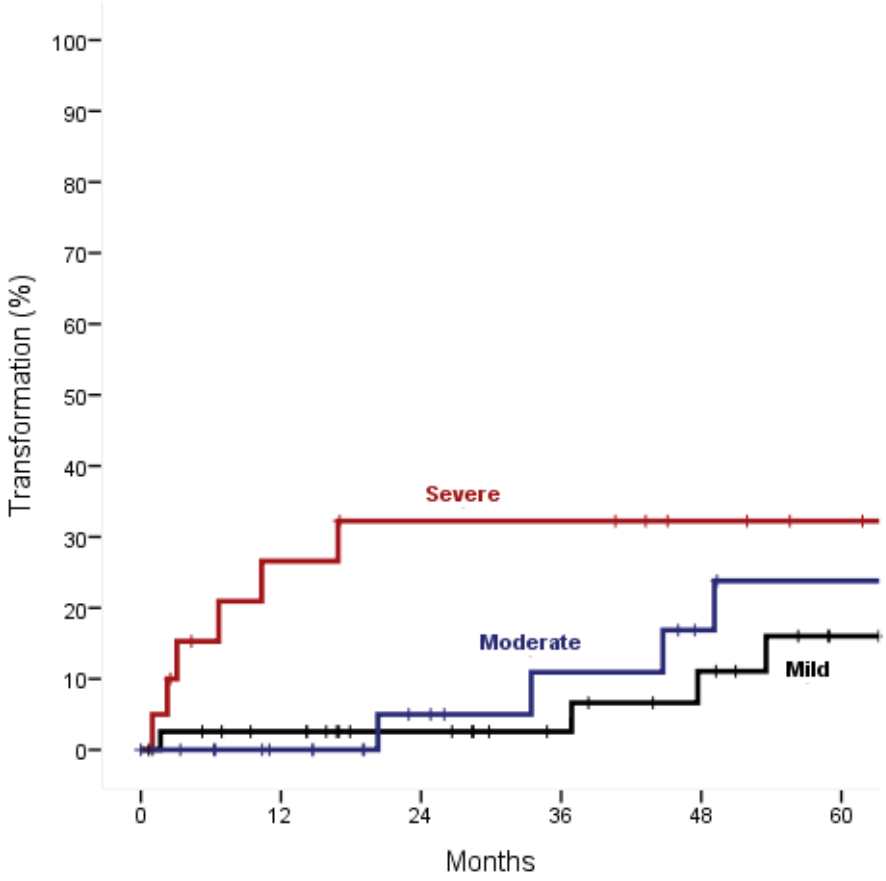

Figure 4 Kaplan-Meier curves for malignant transformation rates: grade/severity of dysplasia.

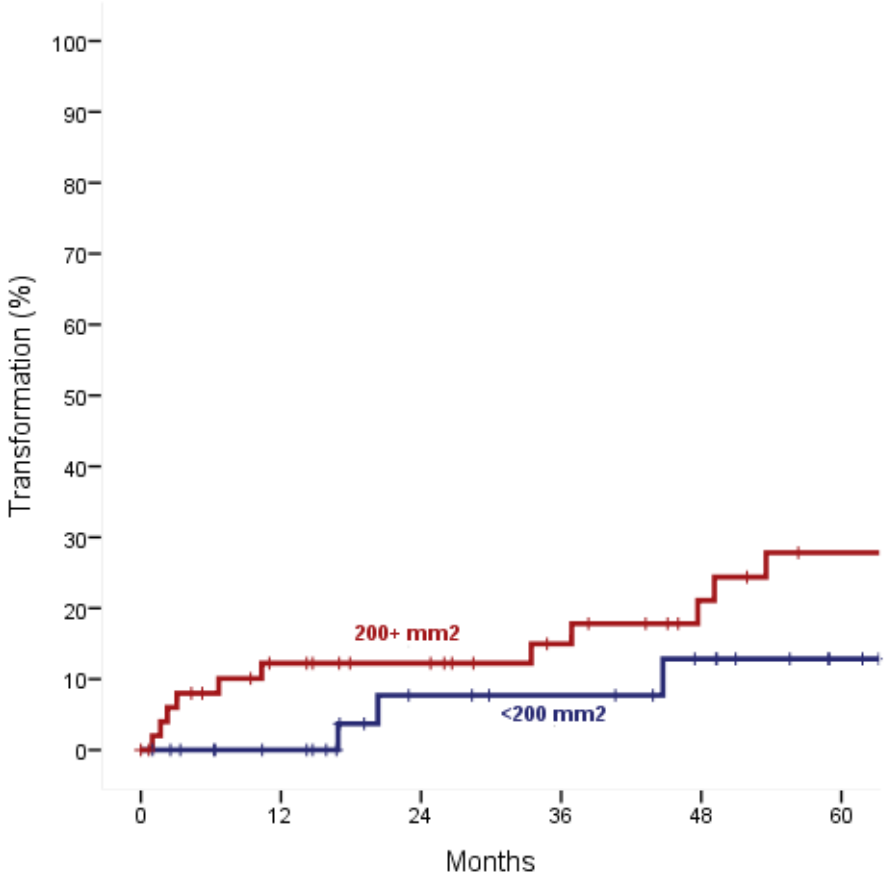

Figure 5 Kaplan-Meier curves for malignant transformation rates: size of dysplasia

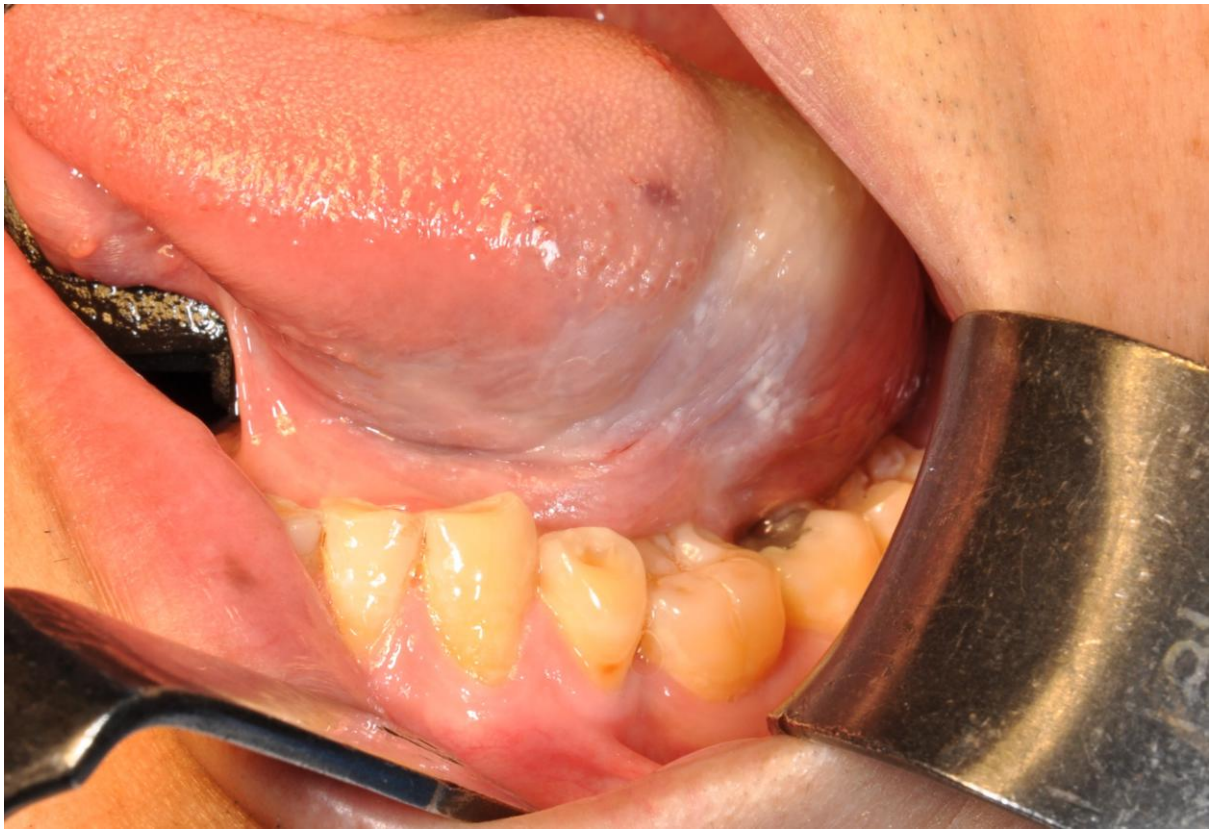

Figure 6: Leukoplakia lateral border of tongue in lifelong non-smoker, histology shows severe dysplasia : high risk of malignant transformation (approx. 40-50%).

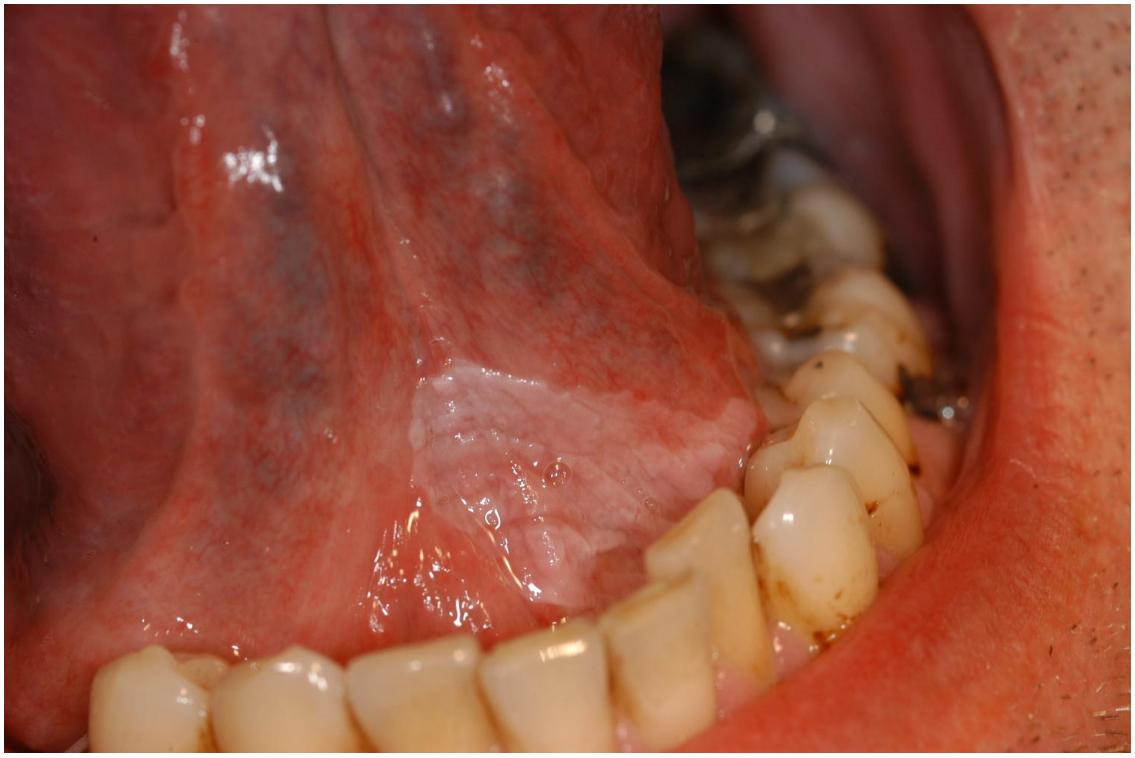

Figure 7: Floor of mouth lesion in heavy smoker with moderate risk (approx. 10%) of malignant transformation