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Histopathological findings of oral epithelial dysplasias and their relation to malignant transformation

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ABSTRACT

Objectives: Oral squamous cell carcinomas (OSCCs) are often diagnosed late. This study aimed to determine how frequently oral epithelial dysplasia (OED) transforms to OSCC and to identify histological features that could influence the rate of malignant transformation.

Materials and methods: The study was a retrospective analysis of OED over 29 years at the Institute of Dentistry, University of Turku, Finland. OEDs with co-existing carcinomas were excluded from the data (5.8%). OED patients who developed carcinoma were identified from the Finnish Cancer Registry database.

Results: Altogether 681 OED patients had a mean age of 59.0 years, and the male:female ratio was 0.67. Of all OED samples, 21.8% were on the tongue, followed by lining mucosa (21.3%), lip (5.3%), and masticatory mucosa (4.85%). In addition, 46.7% had no location cited. The prevalence of mild dysplasia was 62.4%, moderate dysplasia 29.1%, and severe dysplasia 3.2%. Of the patients, 94.7% had an additional histological diagnosis alongside OED. Candidiasis, lichenoid inflammation, and ulcer were found in 18.2%, 0.0%, and 22.7% of severe dysplasias, in 12.1%, 12.2%, and 22.7% of moderate dysplasias, and in 6.6%, 12.2%, and 15.8% of mild dysplasias, respectively. An additional histopathological diagnosis did not increase the risk for OED to transform to OSCC. In a mean time of 5.2 (range 0.7-29.0) years, 7.5% of OED patients developed OSCC.

Conclusions: Location on the tongue and the more severe OED grades increased the risk of malignant transformation of OED. These patients may benefit from an intensified follow-up schedule to ensure early diagnosis of OSCC.

Introduction

By definition, oral epithelial dysplasia (OED) is an epithelial tissue in which the prevalence of squamous cell carcinoma is more likely to appear than in its healthy counterpart [1–3]. In OED, normal maturation and stratification pattern of epithelium are replaced by cytological and/or architectural alterations [2]. OED prevalence is infrequently reported. In a retrospective study by Singh et al. [4], the mean prevalence of OED in the Indian population was 5.7% [4]. According to the literature, the most common site of OED is the tongue and buccal mucosa [4–7]. Habits such as smoking and alcohol consumption are regarded as risk factors for oral squamous cell carcinoma (OSCC), and therefore, for OED [1–9]. Traditionally, OED is graded into three categories by increasing severity: mild, moderate, and severe [10,11]. A newer grading system categorizing OED into two grades, low and high risk, has been suggested in 2017 by the World Health Organization, and it aims to increase objectivity of histopathological grading [1].

OED is a known risk factor for OSCC development, with a malignant transformation rate of 5% to 36% depending on the severity of dysplasia [12–17]. In a meta-analysis by Mehanna et al. [13], the malignant transformation rate for mild to moderate oral epithelial squamous cell dysplasia was 10.3% and for severe oral epithelial squamous cell dysplasia 24.1%. Women seem to have a higher risk for malignant transformation despite OED lesions being less common in females [15,

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18]. Several studies have evaluated how OED grading correlates with OSCC transformation [19–21]. Results vary, from no correlation to a clear correlation [7,19,22]. No consensus of the risk of malignant transformation based on histopathology has been reached [23].

In addition to dysplastic changes themselves, OED often shows other histopathological features such as lichenoid inflammation, candidiasis, or ulcer [18,24-26]. Two studies have reported lichenoid features in OEDs in almost one-third of samples [24,27]. Lichenoid features in chronic inflammation related to OED complicate the diagnosis of dysplasia. Inflammation may cause a dysplastic feature described as reactive epithelial atypia or dysplasia [28]. Despite the presence of lichenoid inflammation in some OEDs, its dysplastic potential and association with malignant potential remain unknown [26,29-31].

The aim of this study was to determine how frequently OED transforms to OSCC in a large cohort of Finnish individuals. To our knowledge, the current study is the largest study conducted in the Nordic countries of this matter so far. An additional aim was to examine other histological diagnoses in OED samples and their potential impact on malignant transformation.

MATERIALS AND METHODS

Patients

A total of 922 OED patients were retrospectively retrieved from the registry of the Department of Oral Pathology and Radiology, Institute of Dentistry, University of Turku, Turku, Finland. OEDs had been diagnosed between the years 1982 and 2011, allowing a minimum follow-up of six years. The dysplasia grading had been done using a three-grade system according to the WHO guidelines at the time of diagnosis. Inclusion criteria were epithelial dysplasia as a histopathological diagnosis (PAD) located in the oral cavity or lips and a referral letter for PAD with a Finnish social security number. The exclusion criterion was concurrent carcinoma (or carcinoma in situ, a diagnosis used before 2017). In order to exclude concurrent carcinoma, OSCCs which had developed within six months time of OED diagnosis, were not included. A sub-analysis of this cohort has been published by Nevanpää et al. [15].

We included the timewise first biopsy sample from each patient (instead of the most severe grade of dysplasia) in order to cover a broader follow-up period. In case a patient had several biopsies taken under the same PAD number, we chose the most severe dysplasia. Information on patients and lesions (sex, age, habits, time of diagnosis, location, previous histopathological diagnosis) was gathered from the referral letters when available. If the same PAD included additional diagnoses (atrophy, candidiasis, lichenoid inflammation, ulcer, sialadenitis, hyperkeratosis, hyperplasia, actinic keratosis, verrucous hyperplasia, and inflammation) besides OED, these were registered and analyzed whether these additional diagnoses have any significance to malignant transformation. The locations of biopsies were inadequately registered in 46% of the samples which is one of the reasons we had to categorize “oral cavity, not otherwise specified (NOS)”. From the statistical point-of-view, simple categorization needed to be made. Oral mucosa can be divided into three main categories based on function and histology; lining mucosa and masticatory mucosa and specialized mucosa of the tongue. We separated lip mucosa from other lining mucosa to rule out possible imprecise information concerning lip by clinician. Dysplasia grades were not re-evaluated since the purpose was to reflect a real-life situation.

Patients who developed OSCC were identified from the Finnish Cancer Registry (FCR) (decision no. THL/1475/5.05.00/2018) by their Finnish social security number. ICD codes C00 and C02 – C06 were considered as OSCC in this study. The follow-up ended on 31 December 2017. This study was retrospective and registry-based. No patient was contacted during the study. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK Dnro: 8l1180112019;324) and Statistics Finland, the Finnish Cancer Registry, and the Institute of Dentistry, University of Turku as a registry holder. Patient consent was waived by the Ethics Committee of the Hospital District of Southwest Finland (ETMK Dnro: 8l1180112019;324).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). The results obtained are considered significant at $p<0.05$. Descriptive variables were calculated as percentages and continuous variables as means with standard deviation. Statistical differences were tested using Chi-square (sex, age, and smoking), Fisher’s exact test (OED grade, age, location, histology, sex, smoking, alcohol consumption, cancer development), the Joncheere-Terpstra test (time to OSCC), and one-way ANOVA (time to malignant transformation). Multinomial logistic regression analysis was used to determine possible predictors of whether a patient developed a cancer. First, the model was executed with all potential predictors, after which the modeling was repeated with statistically significant predictors. Potential predictors were categorized regarding location (lining mucosa, masticatory mucosa, tongue mucosa, oral cavity, and lip), additional histopathological diagnoses, and age at time of OSCC diagnosis. Tobacco and alcohol data were inadequate to allow statistical analysis.

RESULTS

Altogether 681 OEDs fulfilled the inclusion criteria. OED was more common among women (59.8%), and the mean age of patients was 59.0 (range 15-94) years at the time of OED diagnosis (Table 1). Mean age of men was 55.4 and of women 61.8, respectively. The distributions of OED diagnosis by patients’ age and sex, dysplasia location, and dysplasia grade are shown in Figs. 1, 2, and 3, respectively. Mild OED was the most common, constituting over 62% of cases. The severity of dysplasia at first biopsy increased by age (Table 1).

Of the patients, 94.7% (645/681) had an additional histological diagnosis alongside OED. The most common diagnoses were hyperkeratosis (329/681, 44.9%), epithelial hyperplasia (200/681, 27.3%), ulcer (123/681, 18.1%), and epithelial atrophy (90/681, 12.3%). The more specific diagnoses were lichenoid inflammation (61/681, 8.9%) and candidiasis (58/681, 8.5%). A patient could have more than one additional diagnosis. Additional diagnoses were more common in mild

Table 1
Characteristics of oral epithelial dysplasia (OED) patients (n=681).

Patients	N (%)
Men	274 (40.2%)
Women	407 (59.8%)
Mean age at OED diagnosis	59.0 years (range 15-94)
Risk factors	
Smoking (current or ex-smoker) (n=160)	107 (66.9%)
Alcohol consumption (n=26)	17 (65.4%)
Location of OED	
Tongue	149 (21.8%)
Lining mucosa	145 (21.3%)
Lip	36 (5.29%)
Masticatory mucosa	33 (4.85%)
Oral cavity, NOS	318 (46.7%)
Dysplasia grade	
Mild	425 (62.4%)
Moderate	198 (29.1%)
Severe	22 (3.2%)
N/A	35 (5.3%)
Dysplasia grade by age group (<39, 40-59, >60)	
Mild	43 (10.1%), 187 (44.0%), 195 (45.9%)
Moderate	14 (7.1%), 74 (37.4%), 110 (55.6%)
Severe	1 (4.5%), 8 (36.4%), 13 (59.1%)
N/A	9 (25.7%), 11 (31.4%), 15 (42.9%)

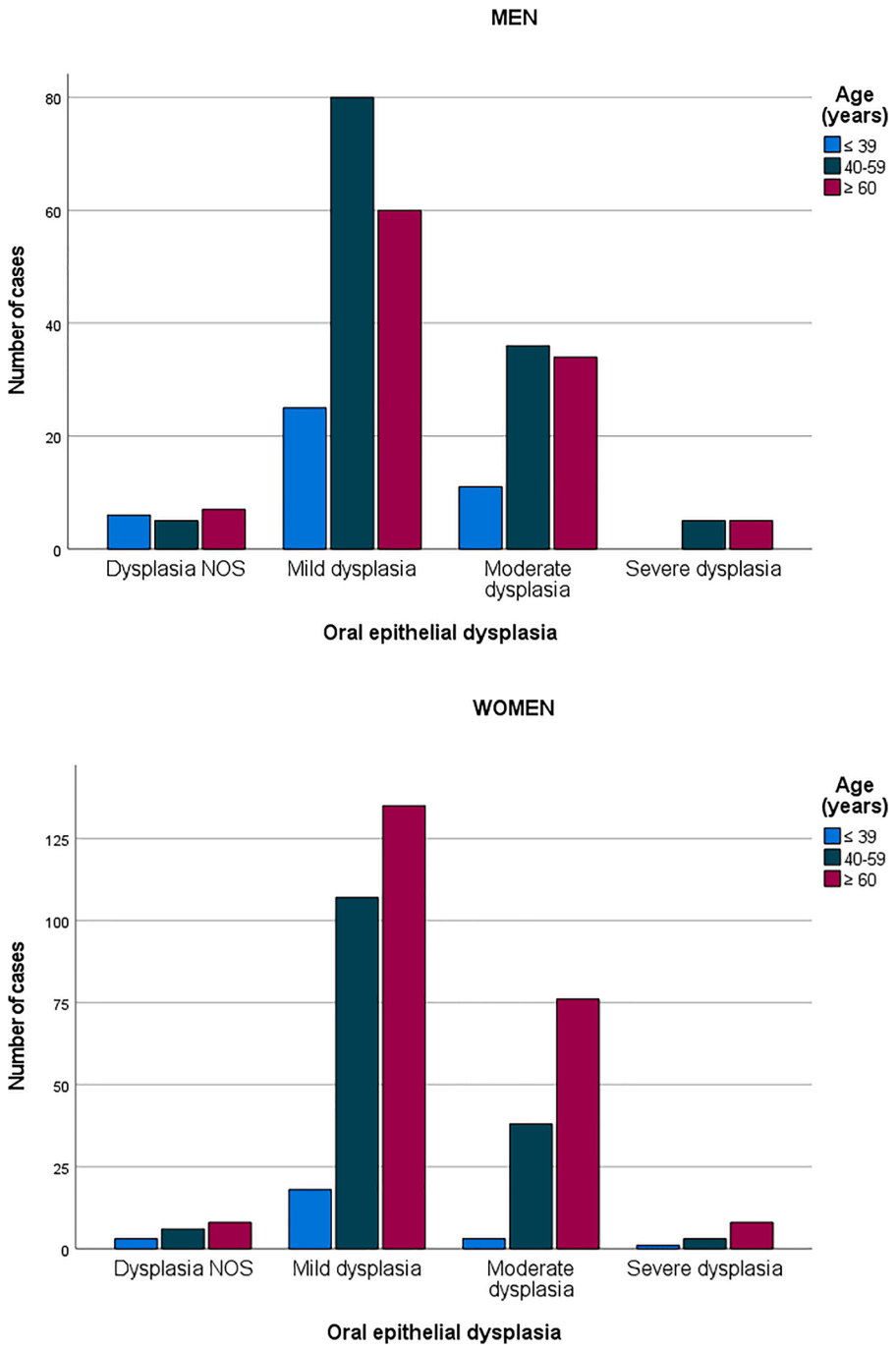

Fig. 1. Oral epithelial dysplasia (OED) distribution by age (≤39, 40-59, ≥60 years) and sex (men, women).

dysplasias than in moderate and severe dysplasias (Fig. 3). However, candidiasis and ulcer were more common in moderate and severe OEDs than in mild OEDs (Table 2).

OED severity (mild, moderate, severe) and its relation to different locations (lining mucosa, masticatory mucosa, tongue mucosa, lip, oral cavity, NOS) were compared (likelihood ratio test p=0.069). When comparing OSCC development with the original OED location, the proportions in lining mucosa were significantly greater than in tongue mucosa in mild dysplasia (p=0.016). Likewise, the proportions in tongue mucosa were greater in lining mucosa in moderate dysplasia (p=0.016). The associations between OED grade and sex or age group were not statistically significant.

Transformation to OSCC

Fifty-one patients (7.5%) developed OSCC. Of these, 59.6% were women and 40.4% were men. The mean age of OSCC patients was 67.1 (range 15-94) years. Five patients (9.8%) were younger than 40 years. Six (11.8%) of the patients were current or ex-smokers. In the entire cohort information of smoking was available for 159 patients. Location of OSCC was available in 98.0% of cases (50/51). Most OSCCs occurred on the tongue (30, 58.8%), followed by the lining mucosa (11, 21.6%). Nine patients (17.6%) developed OSCC on their masticatory mucosa and none on the lip.

When data from both OED and OSCC were available, 62% (31/50) of OEDs progressed to OSCC at the same site. The mean time of malignant transformation from OED to OSCC was 5.2 (range 0.7-29.0, SD 6.25)

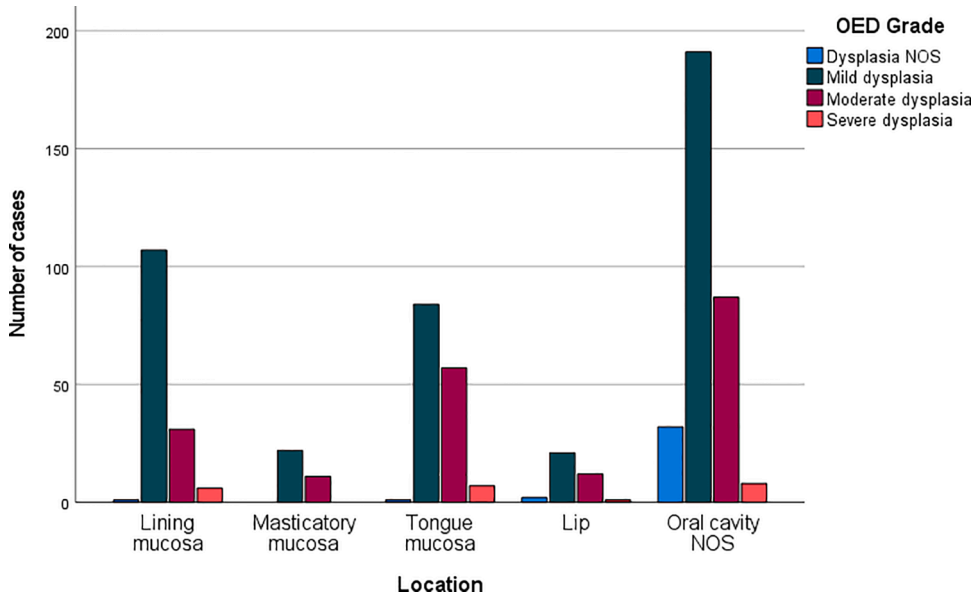

Fig. 2. Grades of oral epithelial dysplasia (OED) according to location.

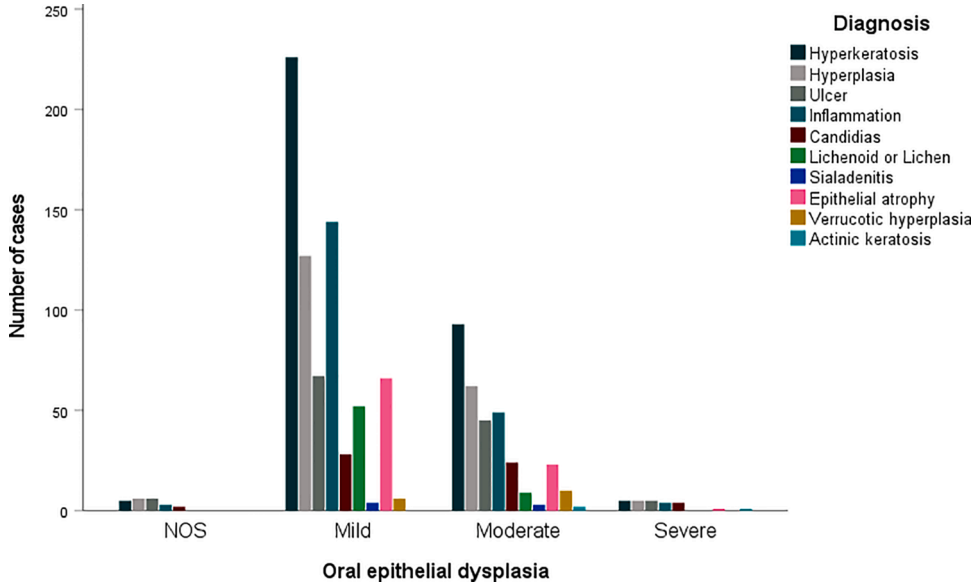

Fig. 3. Additional histopathological diagnosis by OED grade.

Table 2
Additional diagnosis to the diagnosis of oral epithelial dysplasia assigned by the pathologist. Cases of "dysplasia not otherwise specified" are not included.

	Mild dysplasia (n=425)	Moderate dysplasia (n=198)	Severe dysplasia (n=22)
	n (%)	n (%)	n (%)
Candidiasis	28 (6.6%)	24 (12.1%)	4 (18.2%)
Lichenoid inflammation	52 (12.2%)	9 (4.5%)	0 (0.0%)
Ulcer	67 (15.8%)	45 (22.7%)	5 (22.7%)

years when cases developing under 6 months were not considered. Patients with mild dysplasia (24, 47.1%), moderate dysplasia (22, 43.1%), and severe dysplasia (3, 5.9%) developed OSCC. Severity of OED was associated with the risk of OSCC development (HR 3.44, 95% CI 0.83-14.19). Mild dysplasia progressed to OSCC in 4.88 (SD 4.52) years, moderate dysplasia in 3.97 (SD 4.59) years, and severe dysplasia in 2.59 (SD 2.03) years. Dysplasia NOS developed into OSCC on average in 26.2 (SD 3.98) years. Progression times between these groups differed significantly, with more severe OED associated with a shorter time to OSCC development (Joncheere-Terpstra test, p=0.025). Within OSCC patients, 11 (21.6%) had additional diagnoses at the time of OED diagnosis; one patient (2.0%) had candidiasis, eight (15.7%) ulcer, and two (3.9%) lichenoid inflammation.

Patients' age, sex, location of dysplasia, and all additional histopathological diagnoses were analyzed for a potential association with developing OSCC. None of these had a significant link to developing cancer. In multinomial logistic regression analysis (Table 3), tongue mucosa had 2.4 (OR 1.0-5.0, p=0.042) increased odds for developing OSCC relative to lining mucosa and 3.2 (OR 1.6-6.2, p=0.001) increased odds relative to unspecified oral location and lip. However, no significant difference emerged between the tongue and masticatory mucosa.

Table 3
Summary of multiple logistic regression analysis of patients who developed oral squamous cell carcinoma*

Variable	**OR (95% CI)	***P-value
Age	0.999 (0.98-1.02)	0.910
Hyperkeratosis	1.2 (0.7-2.2)	0.464
Location: masticatory mucosa vs. tongue mucosa	5.3 (0.7-40.1)	0.111
Location: lining mucosa vs. tongue mucosa	2.3 (1.0-5.0)	0.042
Location: oral cavity NOS + lip vs. tongue mucosa	3.2 (1.6-6.2)	0.001

Abbreviations: CI, confidence interval
** OR, odds ratio
*** p-value
* Statistically significant ($P<0.05$).

DISCUSSION

We retrospectively evaluated histopathological findings of a large single-institute cohort of OED patients diagnosed between 1982 and 2011. Besides OED diagnosis, over 94% of the biopsy samples were assigned an additional diagnosis by the pathologist. The most common additional diagnosis were hyperkeratosis and epithelial hyperplasia. An additional histopathological diagnosis did not increase the risk for OED to transform to OSCC. Transformation to OSCC occurred for 7.5% of patients, and the risk was higher in tongue OED patients.

The results from this cohort of OED patients living in Southwest Finland were mostly comparable to earlier studies on OED. Similarly to our study, most reports worldwide have shown that OED appears in the fourth and fifth decades of life [4,5,32,33]. In our study, a female preponderance was seen. Although female predominance has been rarely described, another similar European study and a study from Brazil have shown similar results [33,34]. Most studies have noted OED to be more common in men in Asia [4,32,35-38]. Male preponderance has been seen also in UK [6]. However, an Italian study has shown constant distribution among men and women [7].

In our study, the tongue was the most common site for OED, followed by the buccal mucosa, similar to findings from Asia [4,5]and Europe [6, 7]. Mild dysplasias have been reported to be more prevalent than moderate or severe dysplasias worldwide [5,6,7,33,39], which was seen also in our study. To our knowledge, the prevalence of OED is rarely reported in Europe. In India, the prevalence was shown to be 5.7% [4]. Another retrospective study of 173 cases by Pereira et al. from Brazil [33] reported an incidence rate of 1.8%. The discrepancy between prevalence rates could be explained by risk habits such as tobacco. In India, OSCC is among the most common forms of cancer, with betel nut chewing identified as a risk factor [40]. In Finland, between 1982 and 2011 the most common form of tobacco was the cigarette. In 1990, 34% of Finnish men and 19% of women were smokers. Since then, smoking has decreased markedly in Finland [50]. In the current study, smoking was possible etiological factor in 66.9% of OEDs but in only 11.8% of OSCC cases. However, information on smoking habits was poorly available in referral letters. In this retrospective material, e-cigarettes were not yet widely available. All forms of snuff/chewing tobacco are prohibited in Finland.

According to the literature, OSCC prevalence among the OED patients in India, Asia was 9.9% [4]. In our study, 7.5% of OED patients developed OSCC in 5.9 years. Similar to our study, OSCC develops frequently on the tongue and buccal mucosa also in Asia [35,37,38,42, 43], but the reason remains unknown. The most common site for OSCC (as also for OED) in this study was the tongue which has been reported earlier in UK [6]. OSCC developed in the same site as OED in 62% of patients, but the actual sites were not reported in every case. According to the field cancerization theory, in case of OED the risk for OSCC concerns the whole oral cavity [15]. In our study, the mean transformation time from OED to OSCC was 5.9 years, which is longer than previously described (3.3-4.6 years) [41,22]. In addition, the mean age at the time of OSCC diagnosis was higher than described in the literature [36,38, 43,44]. However, one long-time follow-up study from another Western country the UK [34] reported a higher mean age similar to our study. The differences between studies most likely represent influences of cultural factors and habits (such as heavy smoking and/or different tobacco products) but partly also random events.

Three- or even two-scale grading of OED does not imply the continuous progression of dysplasia and poorly predicts the malignant potential of OED [45,46]. It has been suggested that besides OED diagnosis an additional diagnosis could add value to the evaluation of behavior of the lesion [34]. This is further challenged by the demand to characterize cellular changes related to chronic inflammation without certainty of its evolution [28]. True epithelial atypia versus reactive atypia is a debatable topic [28,47]. To study the relevance of additional histological diagnoses in relation to malignant transformation of OED, we analyzed the additional histopathological diagnosis with OEDs. An additional histopathological diagnosis was found in more than 94% of OED samples. Lichenoid inflammation, candidiasis, and ulcer, all associated with inflammation, were identified in 38% of samples. Lichenoid inflammation manifested in mild dysplasias more often than in moderate or severe dysplasias. Chronic inflammatory conditions, such as oral lichen planus and lichenoid reaction, are known to have an increased risk for OSCC, although these lesions would not show histological features of dysplasia [22]. The term 'lichenoid dysplasia' and the presence of lichenoid features in OEDs have long been recognized. In 1985, Krutchkoff and Eisenberg tried to create histologic criteria for lichenoid dysplasia, although these criteria have not been established in the diagnostics [48]. Lichenoid histology could potentially mask the features of underlying dysplasia; alternatively, the pathologist might overinterpret lichenoid features as dysplasia [29,48]. In our study, in addition to the lichenoid features of mild OEDs, moderate and severe dysplasias were accompanied more often with candidiasis and ulcer as additional diagnoses. However, no connection was found between an additional diagnosis and increased risk of malignant transformation.

In our study, OED diagnoses were assigned by several pathologists during the 29-year period, and grading of OED is known to be subjective [10,11]. However, our study aims to reflect the situation of real-life diagnostics and clinical work. As a limitation, due to the study design, we did not have information on patients' dental or medical history. In addition, not all of the referral letters provided information on location of OED or risk habits such as smoking and alcohol consumption. Another limitation is that specific diagnoses, such as only candidiasis, lichenoid inflammation, and ulcer, found in different grades of OED were measured and the numbers were too small for reliable statistics. Regarded also as a limitation, this study includes only patients with oral epithelial dysplasia and we have not studied all available biopsies from every patient. Study strengths include a large single-institute material over 29 years with a minimum six-year follow-up for each patient and the Finnish Cancer Registry data, which covers over 98% of all cancer cases in Finland [49].

CONCLUSION

Location on the tongue and more severe OED grade increased the risk for malignant transformation of OED. These patients may benefit from an intensified follow-up schedule. An additional histopathological diagnosis did not increase the risk for OED to progress to OSCC.

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The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest.

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Nothing to declare.

Please state any sources of funding for your research

All sources of funding should be declared as an acknowledgement at the end of the text. Authors should declare the role of study sponsors, if any, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

This study had no sponsors involvement.

Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper. Authors must obtain written and signed consent to publish the case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request". Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions. Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

This study has ethics committee approval and this is noted in manuscript with specific details.

Author contribution

Please specify the contribution of each author to the paper, eg study design, data collections, data analysis, writing, others, who have contributed in other ways should be listed as contributors.

Riikka Ellonen: Data collections, data analysis, writing

Auli Suominen: Data analysis

Jetta Kelppe: Reviewing along the way

Jaana Willberg: Reviewing along the way

Jaana Rautava: Study design, reviewing

Hanna Laine: Reviewing along the way

Statement of clinical relevance

Location on the tongue and more severe OED grade increased the risk for malignant transformation. An additional histopathological diagnosis did not increase the risk for OED to progress to OSCC.

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Declarations of interest

none.

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