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Original Article

Long-term follow-up of oral epithelial dysplasia: A hospital based cross-sectional study



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KEYWORDS

Epithelial dysplasia; Oral; Potentially malignant lesions; Squamous cell carcinoma **Abstract** *Background/purpose*: Oral epithelial dysplasia (OED) is characterized histopathologically by cellular and morphological changes that remain the single most important factor predicting risk for subsequent development of invasive neoplasia. Hence the aims of the present study were to determine the rate of malignant change of OED in a group of patients followed-up for a number of years, and hence determine factors likely to influence this malignant change, and to describe the clinical characteristics of patients who developed recurrence of OED and second dysplastic lesions.

Materials and methods: This is hospital based cross-sectional study of all biopsy reports with histologically confirmed OED between 2012 and 2018 were retrospectivelly reviewed. Results: A total of 359 patients with histologically confirmed OED were reviewed, twenty

(5.5%) of the 359 patients developed an invasive squamous cell carcinoma (SCC) of the oral mucosa over a period of 2 to 274 months with mean transformation time of 3.3 years.

Conclusion: The high risk of malignant transformation of OED seems to be related to patients older than 50 years when lesions were on the floor of mouth with severe dysplastic changes. © 2020 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Oral epithelial dysplasia (OED) is defined as a lesion in which part of the thickness of the epithelium is replaced by

cells showing varying degrees of cellular atypia and maturational disturbances. Various attempts have been made to classify OED. On 2005, WHO, propose classification system which divides OED into mild, moderate, severe

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dysplasia and carcinoma in situ based on assessment for the presence of various architectural and cytologic changes identified on light microscopy. A 2-tier system has been developed more recently by Kujan et al. which categorizes OED into low and high risk of undergoing malignant transformation, in an attempt to make histopathology more practical for the clinician. However, the use of histopathology for the diagnosis and categorization of OED has long been considered contraversal, with poor inter- and intra-observer agreement and low levels of reproducibility, and there is currently no consensus regarding risk of malignant transformation based on histopathology.

Dysplasia within the oral mucosa can be potentially malignant, ultimately giving rise to oral squamous cell carcinoma. Lesions with features of severe oral epithelial dysplasia (OED) and carcinoma-in-situ are particularly liable to become frank malignancies, and to contain chromosomal anomalies similar to those of oral squamous cell carcinoma. 5-7 However the malignant potential off OED can be variable and unpredictable. 8-10 A wide spectrum of additional markers of malignant transformation, principally based upon immunohistochemical assays have been proposed to aid the diagnosis and determine the prognosis of OED lesions, however in general, these have not proven to be reliable or practical. 11-13 and some researcher indicated that combining DNA ploidy analysis with dysplasia grading will give a higher predictive value than either technique alone.14

Thus until better methods of diagnosis become available there is a need to have a greater understanding of the likely behaviour of lesions with OED. Hence the aim of the present study was to examine the long-term behaviour of a large group of lesions with OED, in particular to determine the rates of malignant change, recurrence and development of new dysplastic disease.

Materials and methods

In this hospital based cross-sectional study, all biopsy reports with histologically confirmed OED between 2012 and 2018 were reviewed retrospectively. Clinical, histopathological and risk factor data were recorded for all patients as identified from histopathological records held in the Oral Surgery department.

Data were collected on a standardized form and loaded into a computer database (SPSS version 20). Recorded data included personal information, history of tobacco smoking and alcohol consumption. Details of tobacco use included type of tobacco, daily amount used (expressed as cigarettes per day), duration of habit and, when applicable, number of years since cessation of smoking. Exclusion criteria were previous oral carcinoma, insufficient sample for analysis, or lack of demographic information to obtain follow up data. 359 patients with OED for whom their was sufficient data to assess long-term outcomes were included in the study. Patients were followed up for period of 2-274 months with a mean follow-up time of up to 40 months. Malignant transformation was considered if a histopathologically proven oral squamous cell carcinoma (SCC) arose in the lesion which had histopathological evidence of OED; recurrence of a dysplastic lesion was considered if a second histopathologically proven dysplastic lesion developed at the same site during follow-up while second dysplastic lesions were considered when a new histopathologically proven OED lesion developed at a site different to that of the index dysplastic lesion.

Statistical analysis

The chi-square and Fisher's exact tests were used for statistical analysis of the results with p value considered significant if less than 0.05.

Results

Twenty (5.5%) of the 359 patients developed a SCC of the oral mucosa over a period of 2–274 months with mean transformation time of 3.3 years. Nine of the patients with SCC (45.0%) were male and 11 (55.0%) female. The mean age at time of diagnosis of SCC was 52.6 years with range of (15–84 years). The mean age for males was 57.1 years (range 44–81 years), the mean age for females 49.0 (range 15–84 years). Eleven of the 20 SCC developed in patients older than 50 years (Table 1).

Nine of the 20 SCC (45%) developed from mixed lesions (erythro-leukoplakia), 4 (20.0%) from white lesions, 6 (30.0%) from red lesions and one (5.0%) from an area of

Table 1 Demographic characteristics of 20 patients who developed a squamous cell carcinoma subsequent to oral epithelial dysplasia compared with patients who did not develop malignancy.

Variables	OED v	vith later SCC	OED v	vith no SCC
	No	%	No	%
Age (years)				
< 40	2	10.0	50	14.7
40-50	7	35.0	79	23.3
> 50	11	55.0	210	61.9
Total	20	100.0	339	100.0
Gender				
Male	9	45.0	181	53.3
Female	11	55.0	158	46.6
Total	20	100.0	339	100.0
Ethnic-backgrou	nd			
Caucasian	15	75.0	204	60.1
Indian	2	10.0	21	6.1
Pakistani and	3	15.0	47	13.8
Bangladeshi				
Afro-caribbeans	_	_	4	1.1
Others	_	_	63	18.5
Total	20	100.0	339	100.0
Marital status				
Married	8	40.0	142	53.9
Single	4	20.0	48	18.2
Widowed	4	20.0	32	12.1
Divorced	4	20.0	41	15.5
Total	20	100.0	263	100.0

OED = Oral epithelial dysplasia.

SCC = Squamous cell carcinoma.

ulceration (Table 2). The floor of mouth (40.0%) was the most common site of malignant changes. But of note a significant number of gingival lesions transformed to invasive cancer (P < 0.01). Malignant transformation was uncommon on the dorsal surface of tongue, alveolar ridge and retromolar area (Table 3). Malignant transformation was more likely with lesions already having features of moderate or severe OED (Table 4). Three (15%) of the 20 oral SCCs developed from areas of dysplastic lesions that had previously been surgically excised. However, a significant number (P=0.001) of malignancies developed in lesions treated only with topical antifungal agents (nystatin or amphotericin). Five (25%) of the 20 tumours developed in patients who had only been advised to reduce their tobacco smoking and alcohol drinking (Table 5), their exact compliance with this advice was not known. Sixty-three (17.5%) of the 359 patients had a recurrence of OED and 37 (10.3%) developed additional dysplastic lesions. The majority of these patients were over 50 years of age, there was a slight male predominance in those who had a recurrence of OED but slightly more females than males developed additional dysplastic lesions but the differences were not statistically significant (Table 6).

Recurrence of OED was most commonly associated with (erythroleukoplakias) lesions in contrast to second dysplastic lesions which usually arose in patients with an initial lesions having the appearance of (leukoplakia) (Table 7). The tongue, buccal mucosa and floor of mouth were the most common sites of recurrent or second OED lesions. Patients treated surgically and/or with antifungals were at greater risk of showing recurrence or additional dysplasia. Cessation of tobacco smoking and alcohol drinking habits associated with a decreased risk of recurrence of OED (P < 0.006) (Table 8).

Discussion

Oral epithelial dysplasia characterized by a spectrum of architectural and cytological alterations caused by accumulation of genetic changes, and is associated with the use of tobacco and alcohol. 11-15 The histopathological

Table 2 Clinical type of oral epithelial dysplasia (OED) and subsequent development of squamous cell carcinoma (SCC).

	OED	OED with later SCC		D with i	no SCC
Clinical type of the lesion	No	%	No	%	P value
White patch	4	20.0	166	48.9	0.09
Mixed (white and red)	9	45.0	150	44.2	0.9
Red patch	6	30.0	3	0.8	0.001
Ulcer	1	5.0	17	5.0	0.7
Lump	_	_	3	0.8	_
Total	20	100.0	339	100.0	

P for chi-square test.

OED = Oral epithelial dysplasia.

SCC=Squamous cell carcinoma.

Table 3 Distribution according to site of oral epithelial dysplasia (OED) and subsequent development of squamous cell carcinoma (SCC).

	OED with later SCC		OE	D with	no SCC
Site	No	%	No	%	P value
Floor of mouth	8	40.0	59	17.4	0.01
Gingiva	3	15.0	8	2.3	0.003
Soft palate	3	15.0	20	5.8	0.1
Buccal mucosa	2	10.0	68	20.0	0.2
Lateral border of tongue	2	10.0	21	6.1	0.5
Ventral border of tongue	1	5.0	56	16.5	0.1
Labial mucosa	1	5.0	38	11.2	0.3
Dorsal surface of tongue	_	-	23	6.7	_
Alveolar ridge	_	_	19	5.6	_
Retro-molar area	_	_	25	7.3	_
Commissure	_	_	2	0.5	_
Total	20	100.0	339	100.0	

P for chi-square test.

OED=Oral epithelial dysplasia.

SCC = Squamous cell carcinoma.

Table 4 Histology of oral epithelial dysplasia (OED) and subsequent development of squamous cell carcinoma (SCC).

	OED with later SCC		OED with no SCO		
Degree of dysplasia	No	%	No	%	P value
Mild dysplasia ^a	3	15.0	164	48.3	0.004
Moderate dysplasiab	4	20.0	100	29.4	0.3
Severe dysplasia ^c	11	55.0	75	22.1	0.001
Carcinoma in-situ	2	10.0	_	_	_
Total	20	100.0	339	100.0	

OED=Oral epithelial dysplasia.

SCC = Squamous cell carcinoma.

- a Chi-square = 3.88.
- ^b Chi-square = 0.44.
- ^c Chi-square = 5.57.

diagnosis of OED can be difficult, particularly as there is a need to determine the degree of dysplastic change. ^{16,17} Examination of the sequentially excised specimens may reveal a range of grades of dysplasia in various portions of the same OED specimen, suggesting that incisional biopsy samples may not be representative of the true nature of the lesion and histologic examination of the entire clinical lesion may be necessary for accurate grading of dysplastic lesions. ^{6,17} However it is sometimes practically difficult and/or unjustifiable to excise entire lesions without some knowledge of its pathology, and the clinical appearance may not mirror the histopathological features. ¹⁸

Several studies have been published on the biological behaviour of OED. $^{5,6,8-10,18-32}$ The transformation rates varied between 5% and 36%, and it is evident that 460 (9.21%) of 4992 observed patients developed invasive

Table 5 Treatment method of oral epithelial dysplasia (OED) and subsequent development of squamous cell carcinoma (SCC).

		th later SCC	OEI	D with	no SCC
Treatment methods	No	%	No	%	P value
Surgical excision ^a	3	15.0	207	61.0	0.0001
Antifungal drugs ^b	12	60.0	52	15.3	0.001
Advice to moderate alcohol and tobacco habits ^c	5	25.0	80	23.5	0.8
Total	20	100.0	339	100.0	

OED = Oral epithelial dysplasia.

SCC = Squamous cell carcinoma.

Table 6 Demographic characteristics of patients showing recurrence or additional oral epithelial dysplastic lesions.

Variables	Recurrence $(no = 63)$			Second dysplastic lesions (no $= 37$)		
	No	%	No	%		
Age (years)						
<40	4	6.3	2	5.4		
40-50	16	25.3	10	27.0		
>50	43	68.2	25	67.5		
Total	63	100.0	37	100.0		
Gender						
Male	37	58.7	17	46.0		
Female	26	41.2	20	54.0		
Total	63	100.0	37	100.0		

squamous cell carcinomas within follow-up periods of 20 years (Table 9).

In the present study 5.5% of patients with OED diagnosed histopathologically from incisional biopsies developed a subsequent SCC within 2–274 months after initial diagnosis, with a mean time to malignant transformation of 40 months. This frequency of development of malignancy is less than that of the other comparable studies. 5,6,8,9,20–22,24–26,28–32 (see Table 9). One explanation for this difference might be that the majority of our patient had mild OED, which reported to have a lower risk of malignant transformation potential. 28,29

In the present study oral SCC tended to develop in patients who had had previous severe OED, however, malignancy also arose in patients who had had mild or moderate OED. Hence, like previous studies the degree of dysplasia within lesions may itself alone not be a reliable predictor of prognosis. 12,13,24,33,34

The clinical appearance of lesions was not a helpful predictor of the degree of dysplasia present and the malignant potential of a lesion. Previous studies have suggested certain morphological characteristics are associated

Table 7 Clinical and histological aspects of oral epithelial dysplasia lesions that recurred or developed second lesions.

Variables	Recurrence of OED (no = 63)		Second OED lesion (no = 37)	
	No	%	No	%
Clinical type				
White patch	18	28.5	21	56.7
Red patch	9	14.2	5	13.5
Mixed	36	57.1	11	29.7
Site of lesion				
Labial mucosa	6	9.5	2	5.4
Tongue	20	31.7	11	29.7
Gingiva ^a	2	3.1	2	5.4
Floor of mouth	11	17.4	9	24.3
Buccal mucosa	13	20.6	7	18.9
Other sites ^b	11	17.4	6	16.2
Histology ^e				
Mild	10	16.9	7	18.9
Moderate	16	27.1	14	37.8
Severe	33	55.9	16	43.2
Treatment method				
Surgical excision	16	25.3	20	54.0
Cryosurgery	12	19.0	5	13.5
Laser excision	8	12.6	3	8.1
PDT ^c	2	3.1	_	_
Antifungal therapy	16	25.3	8	21.6
No active treatment°	9	14.2	1	^d .7

OED = oral epithelial dysplasia.

Table 8 Tobacco and alcohol habits of patient with recurrence or second oral epithelial dysplasia lesions (OED) at last clinical appointment.

	Recurrence of OED		Second OED lesion	
	No	%	No	%
Stop smoking and 'drinking	9#	15.2	6 ^ф	16.2
Reduce smoking and drinking	22	37.2	12	32.4
No change of habits	28#	47.4	19 ^ф	51.3
Total	59	100.0	37	100.0

OED = Oral epithelial dysplasia.

with the risk of malignant transformation of OED.^{35,36} In this study 45.0% of malignancies arose from areas of erythroleukoplakic lesions and 30.0% from red lesions a findings similar to the observations of Amagasa.³⁴ Hence, while oral malignancy may arise from areas of pre-existing

^a Chi-square = 5.85.

^b Chi-square = 13.4.

^c Chi-square = 4.32.

^a Gingiva and alveolar ridge combined.

^b Other sites include soft palate, retromolar area.

^c Photodynamic therapy.

^d Patients advised to stop smoking and drinking.

^e Histology only known for 59 cases.

 $^{^{\#}}p < 0.006.$

 $[\]phi$ p < 0.02.

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Table 9 Summary of published cases of oral epithelial dysplasia (OED) that transformed to invasive squamous cell carcinoma. Authors Number of invasive SCC Transformation time (yr.) Transformation rate % Year No Mincer et al.8 1972 45 5 11 up to 8 Banoczy & Csiba¹⁸ 1976 9 68 1-20 Mean 6.3 13.2 Pindborg et al. 9 1977 61 4 up to 7 6.6 Gupta et al. 10 1980 73 6 10 Mean 8.5 8.2 Silverman et al.⁵ 8 1984 22 Mean 8.1 36.4 Vedtofte et al. 19 1987 47 3 Mean 3.9 6.3 Cregg and Cowan²⁰ 1992 135 24 15 years 17.7 Lumerman et al.6 1995 7 up to 6.5 44 16 Cowan et al. 21 2001 165 24 4 vears 15 Hsue et al.²² 2007 166 8 10 years 5 Arduino et al.23 7 2009 207 15 16 years Ho et al.24 2009 24 33 8 Mean 3 years Bradley et al.²⁵ 9.7 2010 1434 139 Warnakulasuriya et al.26 2011 104 5 10 years 5 Liu et al.²⁷ 2011 37 26.8 138 5.1 years Ho et al. 28 2013 91 23 4 years 25 Sperandio et al.²⁹ 2013 201 17 8.5 Brouns et al. 30 2014 88 8 15 years 9 Dost et al.31 2014 368 18 3.3 years 4.7 Wang et al. 32 2014 1143 72 2.8 years 6.30 Present study 2019 359 20 3.3 years 5.5 Total 4992 460 Up to 20 years 9.21 OED = Oral epithelial dysplasia.

SCC = Squamous Cell Carcinoma.

leukoplakia (known to have OED), it seems that malignancy is more likely to arise in lesions with areas of redness. The site of pre-existing OED has been suggested to influence malignant changes. For example the floor of mouth has been reported to be a possible risk site for malignant transformation. 36,37 In the present study the floor of mouth was among the most common sites of malignant transformation and does suggest that clinicians would be advised to consider all longstanding, solitary, non-traumatic lesions in this site as being potentially malignant until proven otherwise. The increased risk of malignant change at this site is further highlighted by report of high rates of loss of heterozygosity on chromosomes 3p, 9p and 17p in oral leukoplakias of the floor of mouth compared with other oral mucosal sites - even when corrected for degree of histopathologically-determined dysplasia.³⁸

Malignant transformation occurred in patients who received different treatment for their OED lesions. Although the rate of malignant transformation was less for lesions that had been surgically excised than managed by non-surgical methods, oral SCC still developed in sites of previously excised OED. The rate of recurrence of OED was lower for lesions treated surgically than those managed non-surgically, hence despite the possible risk of disease as observed in this and other studies.^{5,19} and the absence of any reliable and/or safe non-surgical therapy, 39,40 and excision of OED lesions remains the first, and possible only treatment of such disease. 19 Recurrence and/or malignant transformation may reflect difficulties in determining the margin of lesions, particularly those on the floor of mouth where dysplastic involvement of the salivary gland ducts may not be detected clinically. 41-43

Most patients did not change their tobacco smoking or alcohol drinking habits after treatment - only 15.2% of patients stopping smoking and drinking before development of recurrence of OED, and 16.2% before development of additional OED lesions. These factors were significant in this study with risk of recurrence and development of second OED significantly different between those who stopped these habits and those who continue these habits which indicated the need to encourage all patients to modify there habits when dysplastic lesions were diagnosed and treated. Chiesa and colleagues⁴⁴ found modification of these habits is not significant predictor for development of relapses in operated oral leukoplakia while others found that cancer and other changes developed more frequently in those patients with leukoplakia who did not stop smoking and drinking.45 It is also reported that leukoplakia may disappear if patients stop smoking. 5,33,46

The results of the present study indicate that OED does not invariably progress to carcinoma although it can be difficult to predict precisely the long term behaviour of such disease, particularly when there is moderate dysplasia. Clinical examination together with histopathological evaluation of incisional biopy material does not allow accurate assessment of long term outcome of OED lesions, in addition despite surgical excision, recurrence and/or malignant transformation can still occur (Table 10). There is thus a need for sensitive methods that not only identify dysplasia, but also indicate likely prognosis. Aside from loss of heterozygosity³⁸ it has been suggested that ploidy may be a reliable prognostic marker of oral leukoplakia and OED.⁴⁷ Vital staining with tolonium chloride does not reliably detect mild or moderate OED⁴⁸ and while

Table 10 Follow-up studies on patients with epithelial dysplasia whose lesions were excised.

Authors	No of cases	Cured	Recurred	Developed SCC			
Mincer et al. ⁸	20	10 (50.0%)	7 (35.0%)	3 (15.0%)			
Banoczy et al. 18	45	43 (95.5%)	1 (2.2%)	1 (2.2%)			
Vedtofte et al. 19	61	46 (75.4%)	12 (19.6%)	3 (5.0%)			
Total	126	99 (78.5%)	20 (15.8%)	7 (5.5%)			
SCC — Squamous cell carcinoma							

cytological examination of brush biopsies may provide the clinician with a non-invasive and rapid method of detecting OED it does not provide detail of the likely degree of dysplasia, and thus has no prognostic value.⁴⁹

It is concluded that while the risk of malignant transformation of OED may be approximately 5% there is a need to develop effective methods of predicting long term outcomes of such disease.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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