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Malignant transformation of oral epithelial dysplasia: a real-world evaluation of histopathologic grading

F. Dost, BOralH, MPhil,[a,b] K. Lê Cao, PhD, MSc,[c] P.J. Ford, BDSc(Hons), BDentSt, PhD, GCHEd,[b] C. Ades, MBBS, FRCPA,[d] and C.S. Farah, BDSc, MDSc, PhD, FRACDS (OralMed)[a,b]
The University of Queensland and Queensland Medical Laboratories, Australia

Objective. This study describes the predictive value of oral epithelial dysplasia (OED) grading as an indicator for malignant transformation and progression.
Study Design. The records of an Australian-based pathology laboratory were searched for oral mucosal biopsies with a dysplastic or malignant diagnosis. Examination for an association with progression and malignant transformation without reinterpretation was performed. Analysis was undertaken using hazard ratios and the Fisher exact test.
Results. A total of 368 patients with a diagnosis of OED were included. Twenty-six patients (7.1%) underwent progression or malignant transformation; the annual malignant transformation rate was 1%. No other characteristics were associated with a heightened risk of progression or transformation.
Conclusions. The severity of OED was not associated with risk of malignant transformation, suggesting that the current OED grading system is not useful for predicting patient outcomes or for determining management strategies. Definitive treatment of all OED is recommended, until a more reliable progression/transformation system is developed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:343-352)

Head and neck squamous cell carcinomas are amongst the most aggressive of tumors, with oral squamous cell carcinoma (OSCC) representing the vast majority.[1] The tendency for local and regional metastases owing to the close proximity and uninhibited infiltration of local lymph nodes is high, and this is thought to be the greatest contributor to the morbidity and mortality associated with OSCC. Five-year survival rates are reportedly as low as 9% for some parts of the oral cavity, largely due to late-stage diagnosis when tumor metastasis has occurred (TNM stage IV).[2] Survival significantly increases to between 66% and 85% when OSCC is detected and treated before lymph node infiltration.[2,3] Early detection also improves morbidity accompanying the treatment of OSCC, with late-stage diagnosis associated with poorer quality of life outcomes.[4] Although it has not been previously reported, it follows that diagnosis and management at the "precancerous" stage would further improve survival rates.[5]

OSCC is commonly preceded by a range of tissue and cellular alterations consistent with carcinoma, yet restricted to the surface epithelial layer, termed oral epithelial dysplasia (OED). These changes often manifest in a clinical mucosal lesion.[1,6] Various attempts have been made to uniformly diagnose and discretely categorize the continuous scale of tissue changes that is OED. Many of these systems are based on the classification of precursor lesions of other epithelial sites, including squamous intraepithelial neoplasia of the cervix and the Ljubljana classification of the larynx.[7] These classifications are limited in their suitability for the oral cavity, which presents a unique local environment that affects the development and progression of precursor lesions differently. Smith and Pindborg[8] described the first system of dysplasia classification for the oral mucosa, which was later adapted by Katz et al.[9] The system grades mucosa as presenting with none, slight, and marked dysplasia; however, it has been criticized by some authors for its complexity.[7] The most recently accepted classification developed by the World Health Organization divides OED into mild, moderate, and severe dysplasia and carcinoma in situ.[1] A 2-tier system has been developed more recently by Kujan et al.,[10] which categorizes OED into low and high risk of undergoing malignant transformation, in an attempt to

Statement of Clinical Relevance

This study confirms that the current system of oral epithelial dysplasia grading is not useful for predicting patient outcomes (e.g., risk of malignant transformation) and that until such a system is produced, definitive treatment of all oral epithelial dysplasia is recommended.

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[a]University of Queensland, UQ Centre for Clinical Research, Herston, Australia.
[b]University of Queensland, School of Dentistry, Brisbane, Australia.
[c]University of Queensland, Queensland Facility for Advanced Bioinformatics, St Lucia, Australia.
[d]Queensland Medical Laboratories, Murarrie, Australia.
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make histopathology more practical for the clinician. For both of these systems, diagnosis is based on assessment for the presence of various architectural and cytologic deviations identified on light microscopy.

Histopathology is recognized as the gold standard in the diagnosis of many mucosal diseases and indeed for many other tissue and disease types.[11] In the case of OED, histopathology is also used as a clinical tool to predict the risk of malignant transformation and often guides clinical management and treatment of patients and their mucosal lesions, with clinicians often monitoring milder cases of OED and actively treating through surgical excision those deemed to be severe.[12,13] However, the use of histopathology for the diagnosis and categorization of OED has long been considered imprecise, with poor inter- and intraobserver agreement and low levels of reproducibility.[14-16]

The usefulness of OED grading has been contested in the literature, and there is currently no consensus regarding risk of malignant transformation based on histopathology.[12] Furthermore, most if not all studies examining malignant transformation of OED have been based on reinterpretation of specimens reexamined by pathologists at the time of study and not on the original interpretation of histologic findings by pathologists at the time of diagnosis. The primary aim of this study was to assess the rate of malignant transformation and progression of OED based on pathologists' histopathologic interpretation at the time of diagnosis without any further reinterpretation, in an effort to model a real-world setting. The secondary aim was to identify whether there were any demographic or specimen factors associated with an increased risk of progression either to a higher grade of OED or to OSCC, given these conditions of interpretation.

MATERIALS AND METHODS

A retrospective audit of computerized biopsy reports was conducted at Queensland Medical Laboratories, a major Australian pathology laboratory service based in Queensland, Australia. The organization comprises 22 laboratories that serve the state of Queensland and Northern New South Wales. The central database included reported biopsies of all anatomic locations diagnosed from January 1, 1995. All reports were coded and classified using the Systematised Nomenclature of Medicine, Clinical Terms.

The central database was searched for biopsy reports dated up to May 31, 2012, for all oral sites and diagnoses of mucosal malignancy or dysplasia. Information was collected on gender, age at diagnosis, residence, biopsy location, and histopathologic diagnosis.

Anatomic locations were categorized as buccal mucosa, gingiva, palate, tongue, floor of mouth, and oral mucosa not otherwise specified. The external lip was excluded in this study, because the majority of cancers occurring in this anatomic location are associated with high levels of ultraviolet light exposure in the Australian climate, an etiologic factor that does not contribute to progression or malignant transformation of the remaining oral mucosa.[17] Residence was based on postal code at the time of diagnosis and was broadly categorized into urban and rural. The urban region was further divided into metropolitan Brisbane and regional areas.

Histopathology was based on the final diagnosis reported by the pathologist at the time of analysis. No attempt at reexamining or reinterpreting the specimen was undertaken. Histopathology was categorized using 2 systems based on the final diagnosis and pathologist notes. The first system was based on the currently accepted 3-tier 2005 World Health Organization Classification, which separates dysplasia into mild, moderate, and severe dysplasia/carcinoma in situ.[1] A second classification, based on a binary system proposed by Kujan et al.,[10] was also applied to cases of OED. With this system, OED was classified as being at either low risk or high risk of malignant transformation.

For this study, malignant transformation was a diagnosis of OSCC made at least 6 months subsequent to a diagnosis of OED. Progression was the diagnosis of a higher grade of OED, based on a mild/moderate/severe hierarchy, at least 6 months after the initial lower grade diagnosis. These definitions did not discriminate between oral subsites, as it was not possible to ascertain with absolute certainty whether malignancy or subsequent OED developed within the exact site of previous biopsy, and this fact underscores OED as a field cancerization effect. Six months is the conventional cutoff to account for biopsy sampling bias and coexisting malignancy.[14,18] Where multiple biopsies were undertaken for a single patient within 6 months, the biopsy reporting the highest level of dysplasia was used for analysis. Patients with a history of head and neck cancer were excluded.

To ensure all cases of OSCC were captured, data were also obtained from the Queensland Oncology Repository, which receives compulsory notifications of cancers diagnosed throughout Queensland in the period 1982 to 2008. Cancers that were recorded with an ICD-10 code of C01 to C14 were obtained and crossmatched with cases of dysplasia to ascertain whether a history of head and neck cancer existed and whether a cancer was diagnosed outside the pathology laboratory used in this study. Codes C02 to C06 were considered oral cancers for this study.

Statistical analysis was undertaken using the R software, version 2.15.0, and IBM SPSS software, version 20.0. For each case of OED, person-years at risk were calculated as the time from diagnosis of OED to OSCC

Table I. Characteristics of patients who were biopsied for oral epithelial dysplasia

	n (%)
Total	368
Gender	
Male	221 (57.3)
Female	157 (42.7)
Locality	
Urban	295 (80.2)
Metro	106 (28.98)
Regional	189 (51.4)
Rural	73 (19.8)

development, death, or the end of the study period. Annual malignant transformation was calculated based on methods previously outlined, being the percentage of OEDs that underwent malignant transformation over the mean person-years at risk of the entire sample.[18] Hazard ratios were calculated for risk of malignant transformation compared with a reference group. Univariate analysis (Fisher's exact test) and 95% confidence intervals were employed to determine significance, which was set at a value of $P < .05$.

The study was conducted according to Human Ethics Guidelines approved by the University of Queensland (2007001478) and the Royal Brisbane and Women's Hospital (HREC/10/QRBW/336).

RESULTS

A total of 368 patients were included in the study, with a mean age of diagnosis of 59.5 years (standard deviation, 12.8 years). Amongst these patients, 383 OED biopsies were identified (Tables I and II). Biopsies were reported by 40 different pathologists; however, the majority (n = 225, 58.7%) were reported by 3 pathologists, all with advanced training in oral and maxillofacial pathology. Over 57% of the study population were males, and almost 90% were aged over 45 years. The tongue, followed by the buccal mucosa, was the most common area for dysplasia, with two-thirds of biopsies taken at these sites. Almost 60% of cases were considered low-grade dysplasia.

A total of 1717 cases of oral cancer (excluding lip and oropharynx) were registered among 1692 patients in the Queensland Oncology Repository for the time period 1995 to 2008. In comparison, 876 cases among 746 patients were identified among the records of the pathology center. Crossmatching between the 2 data sources revealed that 485 cancers (55.4%) that were diagnosed at the pathology center were not registered with the Oncology Repository.

Ten patients harboring 11 lesions representing 2.9% of OEDs progressed to a higher level of tissue dysplasia in a mean time of 1.3 years; 2 of these lesions also subsequently developed malignancy (Table III).

Table II. Characteristics of biopsy-confirmed oral epithelial dysplasia

	n (%)
Total	383
Age at diagnosis (y)	
≤45	42 (11.0)
>46	341 (89.0)
Site of lesion	
Tongue	187 (48.8)
Buccal mucosa	68 (17.8)
Floor of mouth	44 (11.5)
Palate	29 (7.6)
Gingiva	24 (6.3)
Oral mucosa NOS	31 (8.1)
Dysplasia grade	
Mild	221 (57.7)
Moderate	85 (22.2)
Severe/CIS	55 (14.4)
NOS	22 (5.7)
Progression*	
Yes	11 (2.9)
No	372 (97.1)
Malignant transformation	
Yes	18 (4.7)
No	365 (95.3)

NOS, not otherwise specified; *CIS*, carcinoma in situ.
*Progression to a higher form of oral epithelial dysplasia; malignant transformation not included.

Malignant transformation was identified in 18 patients (4.7%) in a mean time of 3.3 years (Table IV). Progression to a higher grade of dysplasia and malignant transformation both occurred most commonly among females and in patients aged over 45 years.

Annual malignant transformation rates are reported in Table V. For all oral sites and dysplasia grades, the annual malignant transformation rate was approximately 1%. Transformation rates were highest for the tongue, with 1.4% progressing to malignancy annually.

Unadjusted hazard ratios were calculated to determine if any patient, clinical, or histopathologic features were associated with progression or malignant transformation (Tables VI and VII). No significant associations were found between any patient or clinical factors with progression or transformation. Further exclusion of OED cases that were not reported by pathologists with advanced training in oral and maxillofacial pathology did not show significant associations between progression and any patient or clinical factors.

DISCUSSION

Histopathology has long been used not only as a diagnostic tool but also for its predictive value for precursor epithelial diseases.[19] This study aimed to describe the predictive value of 2 conventional grading systems for OED by investigating long-term outcomes of dysplastic oral mucosal tissue in a real-world setting. The mean

Table III. Characteristics of patients and biopsies that developed a higher grade of dysplasia

			Initial dysplasia				Progressive dysplasia			
No.	*Gender*	*Locality*	*Age (y)*	*Year*	*Grade*	*Site*	*Grade*	*Site*	*Interval (mo)**	*Malignant transformation*
1	M	Regional	66	1999	Moderate	Floor of mouth, NOS	Severe/CIS	Tongue, right ventral	15	No
2	F	Regional	58	2001	Moderate	Retromolar, NOS	Severe/CIS	Tongue, NOS	25	No
3	F	Metro	71	2002	Moderate	Buccal, right	Severe/CIS	Buccal, right	7	No
4	M	Metro	44	2003	Mild	Buccal, left	Moderate	Oral mucosa, NOS	43	No
5	M	Rural	72	2005	Mild	Tongue, right lateral	Moderate	Tongue, anterior	24	Yes
6	M	Regional	56	2006	Mild	Tongue, right	Severe/CIS	Tongue, right lateral	10	No
7	M	Rural	62	2009	Moderate	Tongue, right	Severe/CIS	Tongue, right lateral	11	Yes
8	F	Rural	63	2009	Moderate	Tongue, left	Severe/CIS	Tongue, left lateral	12	No
9[†]	F	Regional	74	2010	Moderate	Buccal, right	Severe/CIS	Buccal, right	6	No
9[†]	F	Regional	74	2010	Moderate	Hard palate, NOS	Severe/CIS	Palate, right	7	No
10	F	Metro	81	2011	Mild	Tongue, NOS	Moderate	Tongue, NOS	7	No

CIS, carcinoma in situ; *NOS*, not otherwise specified; *M*, male; *F*, female.
*Months between first dysplasia and second dysplasia diagnosis.
[†]In this instance there were 2 biopsies of 2 distinct sites within 1 patient.

Table IV. Characteristics of patients and biopsies that developed malignancy following dysplasia diagnosis

			Initial dysplasia					
No.	*Gender*	*Residence*	*Age (y)*	*Year*	*Grade*	*Site*	*Malignancy site*	*Interval (mo)**
1	F	Regional	70	1998	Dysplasia NOS	Tongue, lateral	Tongue, NOS	63
2	F	Regional	51	1999	Mild	Tongue. Lateral	Tongue, left	76
3	F	Metro	65	1999	Moderate	Tongue, right	Tongue, left	43
4	M	Regional	67	2001	Severe/CIS	Buccal, left	Buccal, NOS	69
5	M	Regional	59	2001	Mild	Tongue, NOS	Tongue, NOS	59
6	M	Rural	50	2001	Mild	Gingiva, NOS	Gingiva, lower	89
7	F	Metro	87	2002	Mild	Tongue, right lateral	Buccal, NOS	69
8	F	Regional	51	2003	Moderate	Tongue, right lateral	Tongue, NOS	6
9	F	Regional	49	2004	Moderate	Oral mucosa, NOS	Gingiva, NOS	24
10	M	Metro	41	2005	Mild	Buccal, left	Buccal, NOS	7
11	M	Rural	72	2005	Mild	Tongue, right lateral	Tongue, right lateral	64
12	F	Regional	42	2005	Moderate	Tongue, left lateral	Tongue, left	21
13	F	Regional	63	2006	Dysplasia NOS	Tongue, ventral	Tongue, NOS	9
14	F	Rural	66	2006	Moderate	Tongue, left	Tongue, right lateral	37
15	M	Rural	53	2008	Mild	Tongue, left	Tongue, left	11
16	F	Regional	70	2009	Mild	Retromolar, right	Buccal, right	31
17	F	Metro	47	2009	Mild	Tongue, left ventral	Tongue, left	11
18	M	Rural	62	2009	Moderate	Tongue, right	Tongue, left	28

CIS, carcinoma in situ; *NOS*, not otherwise specified; *M*, male; *F*, female.
*Months between first dysplasia and second dysplasia diagnosis.

age and male-to-female ratio of this population is consistent with previous studies of Western populations.[14,20,21] Approximately half of all dysplasias occurred on the tongue, which also presented with the highest rate of malignant transformation. This is consistent with previous studies, which show the lateral tongue and floor of mouth having the highest rates of OED development and malignant transformation.[18,22,23] The buccal mucosa was distantly the second most common area of OED development in this study (n = 68, 17.8%). Previous studies have reported high rates of oral mucosal lesions at this site, which is likely to be associated with placement of local tobacco and betel products; however, there is no particular propensity for OED development.[18,24-26] An almost 20% rate of OED occurring in the buccal mucosa is in keeping with rates reported by previous studies,[26,27] but there is significant variation.[21] Some authors have reported the soft palate as a high-risk site,[28] but due to the limited data available in pathology reports, discrimination between OED of the hard and soft palate was not possible in the present study. Less than 5% of OED cases underwent malignant transformation at an annual rate of approximately 1%, and approximately 3% progressed to a higher grade of dysplasia. No association was noted between dysplasia grading and malignant transformation. Furthermore, in this population, no association was noted between any other clinical or patient factors and malignant transformation.

The efficacy of histopathologic grading of precursor lesions as an indicator of malignant transformation has long been contested in the literature.[12,18,29] Current

Table V. Site- and grade-specific annual malignant transformation rates

	*n**	*Total*	*Person-year follow-up*	*Annual malignant transformation rate (%)*	*Mean interval (y)†*
Total	18		1941.42	0.93	3.32
Site					
Tongue	13	187	922.50	1.41	3.19
Buccal mucosa	3	68	352.58	0.85	2.97
Gingiva	1	24	135.92	0.74	7.42
Oral mucosal NOS	1	31	156.67	0.64	2.00
Dysplasia grade					
Mild dysplasia/low risk	9	221	1052.25	0.86	3.86
Moderate dysplasia	6	85	472.17	1.27	2.21
Severe dysplasia/CIS	1	55	282.42	0.35	5.75
High risk	7	140	754.58	0.93	2.71
NOS	2	22	134.58	1.49	3.00

CIS, carcinoma in situ; *NOS*, not otherwise specified.
*Number of cases that underwent malignant transformation.
†Mean number of years between dysplasia diagnosis and malignancy.

Table VI. Association of clinicopathologic factors with malignant transformation

	Malignant progression, n (%)	*No progression, n (%)*	*Unadjusted hazard ratio (95% CI)**
Total	18 (4.7)	365 (95.3)	
Gender			
Female	11 (6.8)	155 (93.4)	ref
Male	7 (3.2)	210 (96.8)	0.4868 (0.1929, 1.2287)
			$P = .146$
Age at diagnosis			
≤45 years	2 (4.8)	40 (95.2)	ref
>46 years	16 (4.7)	325 (95.3)	0.9853 (0.2347, 4.1364)
			$P = 1.000$
Residence			
Remote	5 (6.4)	73 (95.3)	ref
Urban	13 (4.3)	292 (95.7)	0.6649 (0.2444, 1.8092)
Metro	4 (3.7)	105 (96.3)	0.5725 (0.1588, 2.0636)
Regional	9 (4.6)	187 (95.4)	0.7163 (0.2479, 2.0702)
			$P = .694$
Site of dysplasia			
Tongue	13 (7.0)	174 (93.0)	ref
Buccal mucosa	3 (4.4)	65 (95.6)	0.6346 (0.1866, 2.1589)
Floor of mouth	0	44 (100.0)	—
Palate	0	29 (100.0)	—
Gingiva	1 (4.2)	23 (95.8)	0.5994 (0.0820, 4.3805)
Oral mucosa NOS	1 (3.2)	30 (96.8)	0.4640 (0.0629, 3.4222)
			$P = .384$
Dysplasia grade			
Mild	9 (4.1)	212 (95.9)	ref
Moderate	6 (7.1)	79 (92.9)	1.7333 (0.6362, 4.7223)
Severe/CIS	1 (1.8)	54 (98.2)	0.4465 (0.0578, 3.4500)
NOS	2 (9.1)	20 (90.9)	2.2323 (0.5142, 9.6913)
			$P = .298$

CIS, carcinoma in situ; *ref*, reference group; *NOS*, not otherwise specified.
**P* value of Fisher exact test.

evidence recognizes carcinogenesis of the epithelium as a multistep, progressive, cumulative process of genetic mutations that culminate in tumor formation and ultimately invasion and metastasis.[29,30] Although OSCC is not linear in its development, there is general agreement that it begins as a simple epithelial hyperplasia and progresses through OED, with more severe dysplastic changes signifying more extensive genetic aberrations.[30] The timeframe for this process is not known, but is thought to be a relatively slow process, with malignant transformation occurring within 10 years.[18] Although this model may suggest that OSCC is an

Table VII. Association of clinicopathologic factors with dysplasia progression

	Dysplasia progression, n (%)	*No progression, n (%)*	*Unadjusted hazard ratio (95% CI)**
Total	11 (2.9)	372 (97.1)	
Gender			
Female	6 (3.6)	160 (96.4)	ref
Male	5 (2.3)	212 (97.7)	0.4455 (0.1389, 1.4284)
			$P = .542$
Age at diagnosis			
≤45 years	1 (2.4)	41 (97.6)	ref
>46 years	10 (2.9)	331 (97.1)	1.2317 (0.1617, 9.3826)
			$P = 1.000$
Residence			
Remote	3 (3.8)	75 (96.2)	ref
Urban	8 (2.6)	297 (97.4)	0.6820 (0.1852, 2.5108)
Metro	3 (2.8)	106 (97.2)	0.7156 (0.1483, 3.4523)
Regional	5 (2.6)	191 (97.4)	0.6633 (0.1624, 2.7088)
			$P = .851$
Site of dysplasia			
Tongue	5 (2.7)	182 (97.3)	ref
Buccal mucosa	4 (5.9)	64 (94.1)	2.2000 (0.6085, 7.9535)
Floor of mouth	1 (2.3)	43 (97.7)	0.8500 (0.1018, 7.0940)
Palate	1 (3.4)	28 (96.6)	1.2897 (0.1562, 10.6491)
Gingiva	0	24 (100.0)	—
Oral mucosa NOS	0	31 (100.0)	—
			$P = .663$
Dysplasia grade			
Mild	4 (1.8)	217 (98.2)	ref
Moderate	7 (8.2)	78 (91.8)	4.5500 (1.3667, 15.1479)
Severe/CIS	0	55 (100.0)	—
NOS	0	22 (100.0)	—
			$P = .298$

CIS, carcinoma in situ; *ref*, reference group; *NOS*, not otherwise specified.
**P* value of Fisher exact test.

inevitable conclusion to OED, this is not the case, even in the absence of definitive surgical intervention. Conversely, malignant transformation may occur despite active treatment and follow-up of mucosal lesions exhibiting OED.[12,29,31]

The grading of OED attempts to convey to a clinician the level of risk of malignancy, based on the progression of carcinogenic tissue change. Grading of histopathology should therefore be based on the natural biologic behavior and validated against a relevant independent outcome, which in this case is malignant transformation.[11] Currently, there is inconsistency in the literature regarding the usefulness of OED grading in predicting malignant transformation.[32] In a comparable population, Warnakulasuriya et al.[18] report annual transformation rates of 1.8% and 5.6% for moderate and severe dysplasia, respectively. The authors concluded that severity of OED was significantly associated with an increased risk of malignant transformation. These findings are supported by those of Schepman et al.,[33] Silverman et al.,[34] and Liu et al.,[35] who report higher rates of transformation among moderate, severe, and high-grade dysplasia. However, there are an equal number of studies reporting no association between transformation rates and dysplasia severity.[14,21,22,25] Moreover, the presence of OED has been reported by some authors as an insignificant factor in predicting malignant transformation, with high rates of progression in tissue exhibiting a history of epithelial hyperplasia only.[24,25,31,36] But this may simply reflect the unpredictable timeframe of carcinogenesis as well as treatment and follow-up patterns.

Generally, mild cases are monitored, and more severe cases are excised.[12,13] This routine management strategy attempts to reduce the transformation risk of severe OED by removing the transformed field of epithelial tissue. Selectively managing more severe cases aggressively makes the natural progression of OED more difficult to assess, and the biases introduced by treatment are difficult to account for. In a recent systematic review, Mehanna et al.[37] reported that excision of OED reduced the risk of malignant transformation but did not eliminate the risk completely. Conversely, a 2006 Cochrane review reports that there is no evidence to support surgical excision as an effective treatment for the prevention of malignant transformation, but this study focused on oral leukoplakia only.[38]

Holmstrup et al.[31] report a higher rate of malignant transformation among surgically treated oral potentially

Table VIII. Summary of key studies investigating malignant transformation of potentially malignant disorders of the oral cavity

		Patients		Malignant transformation,	Observation period	
Author (year)	*Country*	*Histologic diagnosis*	*n*	*n (%)*	*Years*	*Mean/median*
Banoczy (1976), Banoczy (1977)	Hungary	OED	68	9 (13)	1-30	9.8
		No dysplasia	602	31 (5)		
Silverman (1984)	United States	OED	22	8 (36)	—	7.2
		No dysplasia	235	37 (16)		
Lumerman (1995)	United States	OED	44	7 (16)	>1-9	1.5
Schepman (1998)	Netherlands	Mod OED/Sev OED	47	11 (23)	>1-17	2.5
		No dysplasia/Mild OED	62	3 (5)		
Cowan (2001)	Northern Ireland	OED	165	24 (15)	20	—
		No dysplasia	1182	17 (1)		
Hsue (2007)	Taiwan	OED	166	8 (5)	10	—
		No dysplasia	1297	36 (3)		
Arduino (2009)	Italy	OED	207	15 (7)	16	—
Ho (2009)	Taiwan	OED	33	8 (24)		3
		No dysplasia	115	15 (13)		
Warnakulasuriya (2011)	Southeast England	Mild OED	104	5 (5)	10	—
		Mod OED	70	11 (16)		
		Sev OED	30	8 (27)		
		No dysplasia	1153	11 (1)		
Brouns (2013)	Netherlands	No OED	88	8 (9)	15	1
		Mild/Mod OED	40	6 (15)		
		Sev OED	16	2 (13)		

OED, oral epithelial dysplasia; *Mod*, moderate; *Sev*, severe.

malignant lesions (13%, versus 4% of nonsurgically treated), suggesting that complete excision does not eliminate the risk of subsequent OSCC development. Given the nonrandomized nature of the study by Holmstrup et al., which only undertook complete excision of dysplastic oral mucosal lesions and those presenting in high-risk sites, these findings should be interpreted with caution. Statements such as those made by Balasundaram et al.,[39] describing a growing body of evidence to support a view that excision of OED may induce malignant transformation, are incorrect and misleading. Balasundaram et al.[39] reference both the Holmstrup study[31] and a single outdated animal study[40] as verification of their view, and they fall short in reporting the limited generalizability of these studies and indeed fail to highlight other studies supportive of this notion. Although excision does not entirely eliminate risk of transformation, it does reduce the risk by removing the visible manifestation of dysplastic mucosal fields.[37]

Holmstrup argues that there is a desperate need for randomized clinical trials to ascertain whether surgical treatment is effective in justifiably reducing risk of malignant transformation of OED and further argues that the blind surgical management of patients is more unethical than conducting these large-scale randomized clinical trials.[41] We posit that short of stripping the entire mucosal surface of the oral cavity and removing the entire dysplastic field, there is currently no way to definitively ensure that risk of transformation is significantly reduced or eliminated. This concept is supported by Mehanna et al.[37] in their meta-analysis, which states that removing dysplasia reduces but does not eliminate risk of OSCC formation. From both a clinician and patient perspective, removal of overt, clinically evident dysplasia seems both reasonable and feasible. To date, clinical recognition of OED has been challenging, and ongoing surveillance of these lesions may be regarded as an ineffective treatment option.[21,24,27,41] Of particular concern are homogeneous leukoplakias, which are especially problematic in their management. Leukoplakia patches are idiopathic lesions that may only be diagnosed in the absence of causative factors and carry an increased risk of OSCC development compared with normal mucosa.[1] This current definition excludes such white lesions as traumatic or smokers' keratosis, which do not carry an excessive risk of OSCC. Historically, however, these conditions were classified as leukoplakia in large-scale epidemiologic studies, despite their benign nature, resulting in an artificially low rate of OED and OSCC. This has resulted in a general, perhaps inaccurate, consensus that homogeneous leukoplakia lesions, by current definitions, have low rates of OED and transformation.[6] Furthermore, the definition of leukoplakia implies a heightened risk of OSCC. This contradicts entirely the choice of surveillance as a first-line management option for true leukoplakia. In a recent study, we report an almost 50% rate of OED among homogeneous leukoplakia and present a standardized system for the

management of oral potentially malignant disorders at first presentation.[46] This may also be adapted and applied to surveillance of potentially dysplastic lesions.

With regard to malignant transformation, the proportion of cases that underwent transformation in the present study is considerably low, with previous studies reporting between 5% and 36% of all cases developing malignancy (Table VIII).[14,18,20,21,23-26,34,36,42] In an effort to eliminate bias introduced by the pathologist's interpretation of OED grading, previous studies standardized the diagnostic criteria for OED and reanalyzed each specimen. A recent meta-analysis reported an annual malignant transformation rate of OED of 12.1%.[37] Of a possible 28 relevant studies, half were excluded due to lack of histopathologic diagnosis, lack of segregation of dysplastic and nondysplastic mucosal lesions, and short follow-up. In the present study no attempt was made to standardize or reclassify OED diagnoses or grading, as these findings are arguably more reflective of actual clinical outcomes. Bosman[43] makes a distinction between research histopathology and applied histopathology, indicating that both are essential for diagnosing and managing patients with dysplastic changes. A study by Tilakaratne et al.[19] in 2011 assessed the level of agreement between pathologists in determining the presence of various histopathologic features of OED that are commonly used throughout several classification systems. Intraobserver variability remained high among individual pathologists for the majority of dysplastic features; however, interobserver consistency was poor between pathologists.

In the current study, specialist training in oral and maxillofacial pathology did not significantly affect transformation rates. Qualitative scrutiny of biopsy reports also revealed that diagnostic terms varied significantly outside of conventional terminology (mild/moderate/severe and low/high risk), suggestive of the complexity of categorizing a continuous scale of changes into a discrete, arbitrarily discriminated diagnosis. This has led to several revisions of OED classification, with the most recent being less than a decade old.[1] A consequence of this has been difficulty in comparing studies across time, which produces challenges in interpreting current evidence. Furthermore, with each new diagnostic classification revision, the burden on pathologists (who have a responsibility to adopt these changes and to ensure that they remain current) increases. Evidence would suggest, however, that those in the health services field are slow to adopt innovation, which affects the diagnostic value of these ever-changing classifications.[44]

Histopathology is a useful tool employed by clinicians to guide treatment of mucosal disease by predicting the risk of adverse outcomes. In the case of OED, the current study did not find a significant association between the severity of OED and malignant transformation, a finding suggestive of the complex nature and biologic behavior of this condition and associated oral potentially malignant disorders. It is plausible that more severe cases are treated more aggressively by wider excision and therefore the likelihood of transformation is reduced. Furthermore, given the arbitrary and subjective nature of OED grading, the initial diagnosis may have been inaccurate.

Reexamination of tissue specimens with calibrated pathologists and taking a research rather than applied histopathology approach may increase the significance of OED grading, but this does not seem to represent a meaningful strategy that can be applied by clinicians for patients in most real-world situations. Furthermore, many OSCCs diagnosed within the pathology laboratory were not identified in the Oncology Repository, suggesting that there may be cases of transformation that may have been diagnosed within other laboratories and not identified in this study. The Oncology Repository requires compulsory notification of all malignancies, excluding external skin, with penalties imposed for non-notification.[45] It is anticipated that the rate of transformation would increase slightly if other pathology laboratories were assessed for cases of OSCC.

CONCLUSION

Given the consistent lack of a meaningful correlation of OED severity with patient outcomes in this study and many others, it appears only prudent to undertake more definitive treatment of oral potentially malignant lesions exhibiting any grade of dysplasia (rather than to limit this approach to severe cases) and accordingly to discontinue the "wait and watch" approach currently used for milder cases. This is a function of the poor predictive value of OED grading, which until refined and deemed a useful clinical tool to help predict transformation cannot be used reliably as a guide for treatment decision making. Although complete excision of OED may be considered by some as overtreatment, monitoring of retained overt dysplasia over time is placing patients at risk of harm, given the uncertainty and difficulty of gauging changes in the clinical appearance of such lesions.

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Reprint requests:

Camile S. Farah, BDSc, MDSc, PhD
University of Queensland
UQ Centre for Clinical Research
Building 71/918, Royal Brisbane & Women's Hospital Campus
Herston, QLD 4029
Australia
c.farah@uq.edu.au