Outcomes of surgical management of dysplastic oral mucosal lesions versus observation: A systematic analysis

Pelin Güneri[1]*, Ellie Maghami[2], Hayal Boyacıoğlu[3], Allen S Ho[4,5] and Joel B Epstein[2,5]

1Department of Oral and Maxillofacial Radiology, School of Dentistry, Ege University, Bornova 35100, Izmir, Turkey

2Division of Otolaryngology-Head and Neck Surgery, City of Hope, 1500 East Duarte Road, Duarte, CA, USA

3Ege University Faculty of Science, Department of Statistics, Bornova 35100, Izmir, Turkey

4Department of Surgery, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles CA, USA

5Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles CA, USA

Abstract

Background: The aim was to investigate the outcomes of surgical management versus observation of dysplastic oral mucosal lesions.

Method: Twenty-one papers met the a priori inclusion criteria, resulting in a total of 1943 lesions in 1599 patients. Epithelial dysplasia was grouped as "low-grade" and "high-grade". Clinical outcome was established as the proportion of lesions with complete response, partial response, no response, malignant transformation, and recurrence/new lesions. Data on surgical intervention versus no treatment/observation was statistically analyzed.

Results: Surgical management was provided in 80% of all lesions, versus observation in 20%. Following removal of lesions reported in studies without dysplasia, low grade dysplasia was reported in 59.9% of the oral potentially malignant disorders (OPMDs), and high-grade dysplasia in 40.1% of lesions. In the analysis, overall malignant outcome was 4.99%, and was similar in both the observation and surgical management groups (p = 0.554). The overall successful outcome (complete and partial responses) for all treatment was 45.31%, persistence or recurrences were observed in 27.99% of all OPMDs. In low grade lesions, there was no correlation between the complete or partial responses (p = 0.446), and the number of malignant transformation and recurrences/new lesions (p = 0.310). Similarly, in high grade lesions, no correlation was observed between the complete or partial responses (p = 0.140), and the number of malignant transformation and recurrences/new lesions (p = 0.673). Further analyses revealed no differences between the outcomes of surgical treatment and observation in low risk group (p = 0.358) and in high risk group (p = 0.258).

Conclusion: This analysis shows that OPMDs treated by either surgical removal or observation alone have similar risks of malignant transformation irrespective of the degree of dysplasia, indicating the need for active surveillance of all dysplastic OPMDs.

Introduction

Varying presence of cellular atypia and tissue dysmaturation restricted to the epithelium are termed oral epithelial dysplasia (OED) [1-3], or oral intraepithelial neoplasia (OIN) [4]. According to the severity of the cellular alterations and the thickness of the epithelium involved [1,3,5], lesions may be classified histologically as squamous hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia and carcinoma-in-situ (CIS) [6-10]. Across all degrees of dysplasia, an overall annual malignant transformation rate (MTR) is < 1% per year, and overall risk of malignant transformation is estimated as 3.5% [11-13], whereas 39% of oral dysplasia may regress in follow-up without treatment [10].

Oral dysplastic aberrations may be seen in oral lesions which are defined as oral potentially malignant disorders (OPMDs) [7,11,14-17]. Clinical presentations of OPMDs include leukoplakia, speckled leukoplakia, leuko-erythroplakia, speckled erythroplakia, granular erythroplakia [7,11,18,19], erythroplakia [1,5,15], oral lichen planus with dysplasia, and oral submucous fibrosis [1,5,7,15,20].

Scalpel surgery, laser surgery, cryotherapy, photodynamic therapy, topical or systemic medical therapy and observation have been reported among the treatment approaches for dysplastic OPMDs [21-28]. However, the interpretation of the findings of these studies are challenging due multiple factors including differences in study populations, small sample sizes of studies, nonrandomized study design, and limited follow-up periods. These factors also complicate the evaluation of the outcomes of different treatment modalities. Therefore, the aim of the current systematic analysis is to investigate the outcomes of surgical management of dysplastic OPMDs including leukoplakia, erythroplakia, erythroleukoplakia, oral lichen planus, oral lichenoid lesions, CIS and Stage I OSCC versus observation alone.

Materials and methods

The Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guidelines [29] for selection of papers were followed

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for this study. Final decisions on both inclusion and exclusion of the papers were agreed upon by two authors (PG, JBE) prior to the search process.

The initial literature search was conducted using Web of Science, PubMed and Cochrane databases, including reports published until July 2015. The key words used for searching were ("mouth" (MeSH Terms) OR "mouth" (All Fields) OR "oral" (All Fields)) AND ("precancerous conditions" (MeSH Terms) OR "precancerous conditions" (All Fields) OR "premalignant" (All Fields)) AND lesion (All Fields) AND ("therapy" (Subheading) OR "therapy" (All Fields) OR "treatment" (All Fields) OR "therapeutics" (MeSH Terms) OR "therapeutics" (All Fields)). The initial search identified 866 papers; an additional 26 studies were also collected with manual search (Figure 1).

Following elimination of duplicates, 531 papers were selected for secondary screening. Of these, case reports, reviews, animal studies, non-English papers, studies that reported patients with oral lesions without histologically confirmed diagnosis, cross-sectional studies of the prevalence of oral dysplasia, the investigations missing key variables, and studies which do not report the degree of dysplasia were excluded.

A total of 217 papers were selected for further analysis. The following outcome measures were required for inclusion: the number and gender of the patients, the number of lesions, the histologic grade of the lesions (mild, moderate, severe dysplasia, or carcinoma in-situ (CIS)), the treatment method, the follow-up duration, the rate of clinical or histological responses to the treatment, the rate of recurrences, and the rate of malignant transformation to cancer.

Eligibility of the studies obtained from the search was determined independently by two reviewers (PG, JBE) blinded to each other's selections resulting in 26 papers eligible for initial enrollment. In addition to the observation of the lesions, only the treatment methods that aimed at removal of the lesions such as surgery, laser therapy and cryotherapy were included in the investigation. With this final elimination, a total of 21 papers were selected for systematic analysis (Figure 1).

Data were sub-classified by histologic grade of the lesion (mild, moderate, severe dysplasia, or carcinoma in-situ (CIS)). Cases of mild and moderate epithelial dysplasia were combined and named "low grade epithelial dysplasia" and the cases of severe epithelial dysplasia and CIS were combined and recorded as "high grade epithelial dysplasia" as previously recommended [30,31].

Treatment modalities were grouped for data analysis:1) surgery, 2) laser therapy, 3) cryotherapy, 4) observation, 5) combined surgical therapies. The outcome of each therapy was categorized by clinical outcome as total (complete) response, partial response, malignant transformation and recurrences/ new lesions [32]. When more than one treatment was administered on a group of patients, each treatment modality of that paper was analyzed separately as if it were a single investigation. The treatment outcomes were calculated as the proportion, i.e., the number of patients with above-mentioned treatment responses divided by the number of all patients who received treatment.

Descriptive statistics were used for all variables. Mann-Whitney U test, independent sample t test and Pearson correlation analysis were
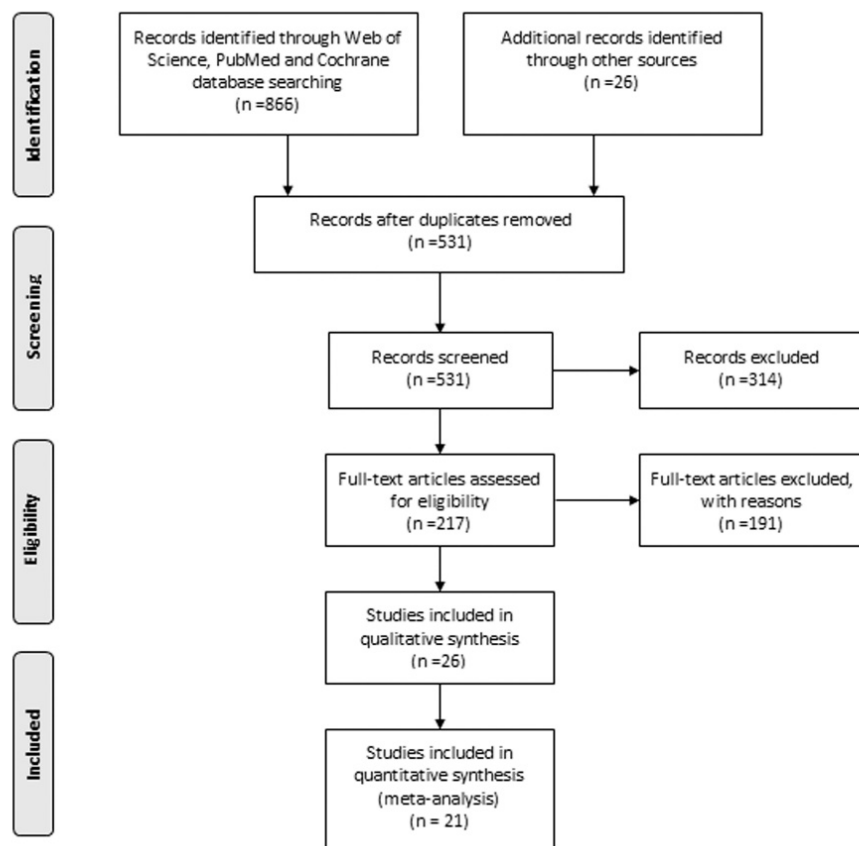

Figure 1. Illustration of anatomic landmarks used for the cephalometric analysis. Sella (S), Nasion (N), Orbitale (Or), Point A: position of deepest concavity on anterior profile of maxilla, Point B: position of deepest concavity on anterior profile of mandible, Pogonion (Pog), Gnathion (Gn), Menton (Me), Anterior Nasal Spine (ANS), Posterior Nasal Spine (PNS), Gonion (Go), Upper Incisor (U1), Lower Incisor (L1), Upper Anterior Facial Height (UAFH): a line connecting Na to ANS, Lower Anterior Facial Height (LAFH): a line connecting ANS to Me.

used to examine differences and correlations among the groups. The statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

A total of 21 papers reporting the treatment outcomes of 1,943 lesions observed in 1,599 patients were analyzed in the systematic analysis. Since various treatment methods were utilized in subsets of patients in some studies [5,10,33-36], each modality was considered as a single investigation, resulting in total number of 30 treatment methods in the analysis.

Descriptive analyses

Of 21 studies, 9 (42.9%) were prospective [15,32,33,36-41] and 12 (57.1%) were retrospective. Laser was the most utilized therapy (36.7%), followed by traditional surgery (26.7%), clinical observation (20%), cryotherapy (10%), and mixed surgical methods (6.7%), respectively. Of those, six utilized CO_2 laser [15,30,39,42-44], three used Nd:YAG laser [37,38,41], whereas two utilized both [5,45]. Lasers were applied for lesion ablation except in one study [39], where resection by undercutting of the lesion was performed.

The mean follow-up duration was 57.63 months, ranging from 12 months [32] and 132 months [5]. Smoking and alcohol consumption were reported in 66.7% of the papers; the number of current/ever smokers ranged between 11.5% and 86%, whereas alcohol users ranged between 10.5% and 83% [5,10,15,30,33,35,37,39,41,42,44,46-48].

Of the included studies, 16 studies (53.3%) evaluated oral leukoplakia (OL) lesions only [30,32-34,36,38,40,41,43-46], and 14 studies (46.7%) were completed on other OPMDs (O-OPMD) including combination of leukoplakia, erythroplakia, erythroleukoplakia, CIS, Stage I OSCC, oral lichen planus, oral lichenoid lesions [5,10,15,35,37,39,42,47,48].

In the studies, all investigated parameters were comparable between OL lesions and O-OPMDs (time to recurrence or transformation ($p = 0.479$), complete response ($p = 0.797$), partial response ($p = 0.05$), malignant transformation ($p = 0.617$), recurrence ($p = 0.286$)).

Among O-OPMD lesions, $5.41 \pm 1.26\%$ and of OL lesions, 4.57 ± 1.53 had malignant transformation. The differences between MTRs of two groups was not statistically significant ($p = 0.617$). Of O-OPMDs, $23.60 \pm 3.89\%$ recurred during the follow-up, whereas this rate was $22.52 \pm 7.89\%$ for OL lesions ($p = 0.286$).

Analyses according to dysplastic grade of OPMDs

When all lesions were considered, 54.48% presented with low grade dysplasia, 21.98% had high grade dysplasia, whereas 23.54% had no dysplasia. Among oral leukoplakia lesions (OLs), 53.37% were within the low-grade dysplasia and 16.29% were within the high-grade dysplasia groups. Of OPMDs including combination of leukoplakia, erythroplakia, erythroleukoplakia, CIS, oral lichen planus and oral lichenoid lesions which were referred as other OPMDs (O-OPMDs), 55.75% presented with low grade and 26.89% with high grade dysplastic lesions, respectively (Table 1). In this systematic analysis, only lesions with histologic grading of dysplasia were included and benign lesions were excluded from the analyses.

The number of low-grade lesions in OL and O-OPMDs were similar ($p = 0.632$), as with that of the high-grade dysplasia lesions including severe dysplasia and CIS ($p = 0.212$)). There was no correlation between the complete or partial responses in low grade lesions ($p = 0.446$), and the number of malignant transformation and recurrences/new lesions ($p = 0.310$). Similarly, no correlation was observed between the complete or partial responses in high grade lesions ($p = 0.140$), and the number of malignant transformation and recurrences/new lesions ($p = 0.673$) (Table 2).

Table 1. The risk groups, follow-up durations and overall treatment outcomes (observation, conventional surgery, laser surgery and cryosurgery) in oral leukoplakia (OL) and oral premalignant disorders (O-OPMDs)

		N	OL	O-OPMD	P value	Total
Degree of dysplasia	**Low**		16	14		30
		Mean	0.53	0.56	0.632	0.54
		Std.Dev.	0.28	0.26		0.27
	High	N	11	13		24
		Mean	0.16	0.27	0.212	0.22
		Std.Dev.	0.12	0.19		0.17
Treatment outcomes	Complete response	N	13	8		21
		Mean	0.42	0.38	0.797	0.41
		Std.Dev.	0.40	0.39		0.39
	Partial response	N	9	8		17
		Mean	0.00	0.09	0.05	0.05
		Std.Dev.	0.00	0.14		0.10
	Malignant transformation rate	N	11	11		22
		Mean	0.05	0.05	0.617	0.05
		Std.Dev.	0.05	0.04		0.05
	Recurrence	N	10	8		18
		Mean	0.23	0.24	0.286	0.23
		Std.Dev.	0.25	0.11		0.19
Time to recurrence/malignant transformation		N	9	6		15
		Mean	52.01	42.9	0.479	48.37
		Std.Dev.	39.49	33.10		36.11
Follow-up duration (months)		N	16	14		30
		Mean	37.31	78.80	0.000	56.67
		Std.Dev.	15.13	36.21		33.90

Table 2. Comparison of the outcomes of the treatment modalities used for OL and O-OPMDs (*p* values)

Treatment methods	Complete responses	Partial responses	Malignant transformation rate
Observation- Conventional surgery	0.851	0.573	0.624
Observation-Laser	0.93	0.04	0.251
Observation-Cryotherapy	0.313	0.182	0.127
Conventional surgery-Laser	0.933	0.391	0.109
Conventional surgery-Cryotherapy	0.423	0.541	0.141
Observation-Conventional surgery + Laser + Cryotherapy + Combined surgical therapy	0.726	0.241	0.554

Treatment modalities

In this analysis of dysplastic OPMDs, 68.2% of the lesions received treatment, either surgery, laser therapy or cryosurgery. However, intervention was mostly provided in the prospective studies (91.25%) compared to retrospective investigations (56.67%) ($p = 0.017$).

Malignant transformation was reported in $4.99 \pm 0.97\%$, recurrences were observed in $23 \pm 4.59\%$ of all lesions.

Independent Samples t test and Pearson correlation analyses revealed that complete and partial response rates were comparable between observation and surgical intervention ($p = 0.851$ and $p = 0.537$, respectively). Similarly, the MTR in observation groups was not different than that of the surgery groups ($p = 0.624$) (Table 2).

Observation was associated with fewer partial responses when compared with the results of the laser therapy, ($p = 0.04$), however, the complete response and the MTRs were comparable ($p = 0.930$ and $p = 0.251$, respectively). Observation and cryosurgery also provided similar complete and partial responses, and MTRs ($p = 0.313$, $p = 0.182$ and $p = 0.127$, respectively) (Table 2).

Conventional surgery and laser surgery had similar complete ($p = 0.933$) and partial responses ($p = 0.391$), malignant transformation ($p = 0.109$) and recurrence rates ($p = 0.473$). Similarly, conventional surgery and cryotherapy had comparable complete ($p = 0.423$) and partial responses ($p = 0.541$), malignant transformation and recurrence rates ($p = 0.141$ and $p = 0.924$, respectively) (Table 2).

When the results of all surgical management methods (conventional surgery, laser surgery, cryosurgery and combined surgery) were grouped and the outcomes were compared with those of observation alone, similar complete ($p = 0.726$) and partial responses ($p = 0.241$), malignant transformation rates ($p = 0.554$) and recurrences ($p = 0.960$) were observed (Table 2).

Discussion and conclusion

In the present paper, the recurrence rates were highly variable for OL, as reported previously with recurrence rates ranging from 7.7 to 38.1% [42,43,49-52]. In the current analysis, recurrences were observed in 23% of all treated lesions, within the range reported in the literature.

A subset of OPMDs may progress to OSCC despite active treatment and active follow-up [3,11,35,53-56]. Unfortunately, it is not possible to predict if and when a potential precancerous lesion will transform to cancer [11,34,57-60], since there are no reliable clinical, histological parameters or molecular tests available for clinical use that predict the transformation potential of OPMDs [10,58,60].

The MTR observed in this analysis (4.99%) was within this range. The length of follow-up has been identified as one of the variables in the

MTRs of OPMDs among the studies [53,61]. Malignant transformation has been reported to be between 1.5-10 years [6,20,53] and beyond 20 years [58].

The degree of dysplasia and the anatomical site were the two influential factors in a proposed follow-up schema [16]. Despite these studies showing progression to cancer, it has been suggested that patients who remain disease free for 3 years after treatment may not require follow-up on a scheduled basis [62]. Some authors report that severe epithelial dysplasia increases the risk of malignant transformation [2,9,30,33,50,53-56,63-65]. Thus, follow-up regimens of 6 monthly for lichen planus, leukoplakia/mixed and erythroplakia lesions without dysplasia, 3 monthly for mild/moderate dysplasia, and monthly for severe dysplasia/CIS were suggested [59,66,67]. However, it is important to note that others have not seen an association between the grade of dysplasia and transformation rates [3,10,11,35,43,44]. Even histologically innocuous lesions have progressed to OSCC [9,41,62] and OSCC may arise *de novo* or at different locations than the site of the treated lesions or in the absence of clinically detected mucosal change [30,42,44,61].

There is no general consensus on the treatment of OPMDs [68], and surgery has been reported to have limited or no effect in a number of studies [10,12]. This may be the case as local procedures may not adequately address the extent of molecular change in the epithelium, adjacent connective tissue, nor the oral microenvironment, and potential multiple independent foci of abnormal cells within the epithelium may give rise to development of multiple primary cancers and recurrences [42]. Conversely, it is unclear if dysplasia, when surgically treated, is given consistent management typically afforded in cases of biopsy proven malignancy (wide margins, frozen sections beyond resection), because these approaches are less likely in less severe grades of dysplasia. Even though in our analysis, the papers that preferred surgical management methods utilized a safety margin of 3-5 mm, the variability in surgical management including narrow margins or greater attention to preservation of nearby structures to reduce potential morbidity of treatment, given the limited risk of progression of OPMDs to cancer, may confound the potential efficacy of surgical intervention.

In this paper, the included studies' clinical treatment outcome has been associated with continuing smoking [10,15,30,39,42,48] and alcohol consumption [5,10,30,42], although alcohol consumption [15,33,39,46] and tobacco relation were not clear in some others [33,35,46,47].

Our analysis revealed that lesions with low grade dysplasia behaved similarly to high risk lesions with respect to malignant transformation irrespective of surgical treatment or observation. Similarly, a recent study reported that the treatment outcome is associated with both the inherent nature of the OPMD and the treatment method [69]. The failure of the treatment of a lesion was thought to indicate the aggressiveness and increased malignancy potential, but this assumption was not supported in a retrospective investigation which revealed malignancy did not necessarily develop in treatment resistant lesions [69]. Even though some clinicians prefer to excise severely dysplastic lesions due to potential higher malignancy risk and to observe lesions with mild and moderate dysplasia which possibly have lower risk [70], our systematic analysis showed that patients who received surgical treatment have a similar risk for malignant transformation with those who remained under surveillance without surgical intervention. Among previous studies, only one favored surgical intervention rather than observation

[5], and active treatment and observation groups provided comparable risks for malignant changes [10,33,35]. This has been attributed to the potential triggering effect of surgery on lesion microenvironment and immune and inflammatory mediators [35]. The presence of molecular alterations harbored in oral mucosa are not detectable by clinical or histological examination [16,32,45,61,62,71,72] which complicates the potential of local surgical therapy to cure and prevent new lesions within all at-risk tissue exposed to potential carcinogens [44,71,73].

Several caveats deserve mention that may limit generalizability of our results, including selection and publication bias inherent in meta-analyses. New premalignant or malignant lesions at a different site may not indicate the lack of efficacy of a particular treatment, rather, it may be due to pre-malignant or malignant clones arising or migrating outside of the area of treatment [61]. Another confounder may be inter-pathologist variability in interpretation of identification and grading of dysplasia. Similarly, reversal of the lesions without intervention has been seen and may be associated with the termination of potentially carcinogenic habits, or treatment of superimposed confounding factors such as candidiasis and other local irritants or may represent remission due to immune processes [10,35].

The decision to manage surgically is usually based upon the presence and severity of dysplasia which are assessed following biopsy, the extent of the lesion, the presence of single or multiple lesions, patient anxiety and compliance for follow-up. Therefore, due to the presence of provider bias and study heterogeneity [5,12,46,74] current data is limited in guiding current practice and meticulous follow-up of all mucosal lesions is mandatory [32]. The search for effective approaches for preventive or curative treatment of such lesions include systemic and topical chemoprevention to arrest or reverse the process of malignant transformation is sought but remains to be defined [16,61]. The degree of dysplasia as reported on biopsy may consequently not reflect the natural history of potentially malignant disorders and inclusion of cellular/molecular markers or chromosomal changes continues to be sought to predict the cellular behavior of OPMDs [11,75].

Within the limitations of this systematic analysis, no significant impact upon outcomes of surgical management of dysplastic oral lesions compared to active surveillance was seen. More definitive guidance for management of OPMDs with dysplasia requires collaborative multicenter, prospective, long-term and controlled studies employing well defined clinical and histological criteria.

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