Potentially Malignant Disorders Revisited – The Lichenoid Lesion/ Proliferative Verrucous Leukoplakia Conundrum

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Abstract

Background: Clinically identifiable potentially malignant disorders (PMD) precede oral squamous cell carcinoma development. Oral lichenoid lesions (OLL) and proliferative verrucous leukoplakia (PVL) are specific precursor lesions believed to exhibit both treatment resistance and a high risk of malignant transformation (MT).

Methods: A retrospective review of 590 PMD patients treated in Northern England by CO_2 laser surgery between 1996 and 2014 was carried out. Lesions exhibiting lichenoid or proliferative verrucous features were identified from the patient database and their clinico-pathological features and outcome post-treatment determined at the study census date of 31 December 2014.

Results: 198 patients were identified: 118 OLL and 80 PVL, most frequently leukoplakia at ventro-lateral tongue and floor of mouth sites, equally distributed between males and females. Most exhibited dysplasia on incision biopsy (72% OLL; 85% PVL) and were treated by laser excision rather than ablation (88.1% OLL; 86.25% PVL). OLL were more common in younger patients (OLL 57.1yrs; PVL 62.25yrs; p=0.008) and more likely than PVL to present as erythroleukoplakia (OLL 15.3%; PVL 2.5%; p = 0.003). Whilst no significant difference was seen between OLL and PVL achieving disease free status (69.5% and 65%, respectively; p = 0.55), this was less than the overall PMD cohort (74.2%). MT was identified in 2 OLL (1.7%) and 2 PVL (2.5%) during follow-up.

Conclusion: One-third of PMD cases showed features of OLL or PVL, probably representing a disease presentation continuum. Post-treatment disease free status was less common in OLL and PVL, although MT was infrequent.

Introduction

Potentially malignant disorders (PMD) are clinically discernible oral diseases, most frequently localised mucosal disorders such as leukoplakia, erythroplakia and erythroleukoplakia, but also widespread abnormalities such as proliferative verrucous leukoplakia (PVL) or controversially oral lichenoid lesions (OLL), that precede in an unpredictable manner invasive oral squamous cell carcinoma (OSCC) development[1,2]. Contemporary PMD management is based upon initial incision biopsy to provide histological assessment and severity grading of underlying tissue disorganisation and dysmaturation changes characteristic of epithelial dysplasia, followed by targeted surgical excision for definitive diagnosis and treatment of lesions deemed 'high-risk' for malignant transformation (MT)[3,4,5].

Whilst systematic review has estimated an overall 12% MT risk over a mean period of 4.3 years[6], clinico-pathological features associated with highest cancer risk include appearance of erythroplakia, erythroleukoplakia or PVL, mucosa exhibiting severe dysplastic change and origin on ventro-lateral tongue and floor of mouth sites[3-6]. In addition, in relation to OLL we have demonstrated persistence of disease post-treatment with poor long-term outcome, including an increased MT risk, often in the absence of recognisable dysplasia[3,7,8]. Whilst strict definition remains elusive, OLL are generally characterised histopathologically by the presence of lichenoid inflammation (LI), a band-like lymphohistiocytic infiltrate subjacent to hyperplastic or dysplastic epithelium; the latter finding is sometimes termed 'lichenoid dysplasia'[9,10,11]. However, multiple white hyperkeratotic lesions with a verrucous epithelial hyperkeratosis and 'interface mucositis' are also features of PVL and, by mimicking OLL, contribute to diagnostic confusion[9]. Long-term patient follow-up data are required to improve our understanding of the natural history of these disorders and to try to resolve the conundrum surrounding both diagnosis and management[3].

In a series of recent papers, we have defined and characterised clinical outcome data for a 590 PMD patient cohort undergoing standardised

interventional CO_2 laser treatment, primarily excision surgery but also ablation for small or less dysplastic lesions especially at gingiva and alveolar sites[3,5,12]. Post-treatment, 438 patients from this cohort (74.2%) were disease free (DF), 53 had persistent PMD disease and 99 (16.8%) exhibited either unexpected OSCC on excision (71 or 12%) or developed SCC subsequently (28 or 4.8%) during a mean 7.3 year follow-up period[3,5,12].

The specific purpose of this paper was to revisit this 590 PMD cohort and determine the prevalence of OLL and PVL in the population and to distinguish clinico-pathological features and post-treatment outcome data that might characterise and predict clinical behaviour for these specific PMD sub-groups.

Method

Caldicott Approval previously obtained from Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust facilitated anonymized, retrospective data collection from medical records, operating books and original pathology reports from PMD patients treated by laser in Maxillofacial Surgery between August 1996 and December 2014. Inclusion criteria for this review required new patients with single-site PMD disease and a histopathological diagnosis of LI or PVL. Detailed demographic and clinico-pathological data included: patient age and sex, lesion appearance and site, definitive histopathology diagnosis, treatment intervention (laser excision or ablation), and clinical outcome recorded at original study census date of 31 December 2014.

All biopsies and CO_2 laser surgeries were carried out by the first author (PJT), or colleagues working under direct supervision, to established guidelines and within 6 to 12 weeks of initial presentation to prevent disease progression[3]. Formalin-fixed tissue specimens were assessed via standardized histopathology examination by oral pathologists at the Royal Victoria Infirmary using agreed diagnostic criteria, peer review and consensus grading[3]. The World Health Organization (WHO) system was

used and dysplasia classified as mild, moderate or severe, with diagnoses of hyperkeratosis (HK), LI, and PVL made as appropriate. Clinical outcomes were listed as DF, further PMD disease or MT.

Statistical Analyses

Descriptive Statistics were used to summarise patient demography, clinico-pathological features, clinical outcome and follow-up data. Pearson's Chi-squared tests (P values computed using Monte Carlo simulation with 2000 replications) and logistic regression were used to assess possible associations between clinico-pathological features and post-treatment outcomes; the latter was classified for analysis as DF or further disease (including persistent PMD and MT). All statistical analyses were carried out using the R Environment for Statistical Computing (version 3.2.5, www.r-project.org/).

Results

Overall, 198 out of 590 patients (33.6%) received a histopathological diagnosis of either OLL (118 or 20%) or PVL (80 or 13.6%). Whilst the numbers of OLL diagnoses were reasonably consistent throughout the 18-year period, PVL was more frequently identified during the later years of the study; 68 PVL cases (85%) being diagnosed between 2010 and 2014.

Oral Lichenoid Lesions

Table 1 lists the clinico-pathological details and treatment outcomes for 118 OLL patients: 58 males and 60 females (age range 24-84yrs; mean 57.1yrs). In 99 cases (83.9%), lesions presented as leukoplakia with 19 erythroleukoplakias (16.1%). 66 lesions (55.9%) arose at ventro-lateral tongue and floor of mouth sites, 30 (25.4%) on buccal or labial commissure mucosa, 16 (13.6%) on gingiva and alveolus, with other sites less frequently involved (6 cases or 5.1%). Histopathological diagnoses confirmed that 85 lesions (72%) showed varying degrees of dysplasia upon incision biopsy (40 mild, 29 moderate and 16 severe), whilst 33 (28%) exhibited features of HK

and LI only. Whilst 104 lesions (88.1%) were excised by CO_2 laser, 14 (11.9%) underwent ablative treatment. 82 patients (69.5%) were documented disease free at census, whilst 36 (30.5%) developed further disease; 2 of the latter cases (1.7%) subsequently underwent MT.

Proliferative Verrucous Leukoplakia

Table 2 summarises the clinico-pathological data and disease outcome status for 80 patients exhibiting PVL: 41 males and 39 females (age range 25-94yrs; mean 62.3yrs). Clinically, 78 lesions (97.5%) were leukoplakias with only 2 (2.5%) presenting as erythroleukoplakia. Ventro-lateral tongue and floor of mouth sites accounted for 31 lesions (38.7%), with buccal or labial commissure 21 (26.3%) and gingiva and alveolus 11 (13.7%); tongue dorsum, palate, fauces and labial mucosa sites accounted for a further 17 (21.3%). Histopathological diagnoses showed that 68 lesions (85%) exhibited varying degrees of dysplasia (45 mild, 18 moderate and 5 severe), with 12 (15%) reported as PVL only. 69 lesions (86.3%) were excised by laser and 11 (13.7%) ablated. 52 patients (65%) were DF at time of census, with 28 (35%) developing further disease; 2 of these (2.5%) underwent MT.

Diagnostic Discrepancy

In 10 patients, 3 of which are highlighted in Table 1 and 7 in Table 2, histopathological diagnoses of LI and PVL were both ascribed. In 7 cases this was a ‘same-site’ discrepancy between initial incision and subsequent excision biopsy diagnoses whilst in another 3, further ‘new-site’ disease developed and was diagnosed as PVL or LI in a patient previously categorized by the alternate diagnosis.

Statistical Analyses

In terms of significant differences, OLL were usually seen in younger patients (logistic regression: wald $\chi^2 = 7.09$; $p=0.008$) and more likely than PVL to present as erythroplakia or erythroleukoplakia (Chi-squared test: $\chi^2 = 9.303$; $p = 0.003$). Whilst OLL presented most frequently on ventro-lateral tongue and floor of mouth mucosa, PVL was more evenly distributed amongst all oral sites including tongue dorsum and fauces which were rarely affected by

OLL (Chi-squared test: χ^2 = 16.018; p = 0.013). Table 3 summarizes statistical analyses of OLL and PVL clinico-pathological features that might influence clinical outcome status (DF or further disease) post-treatment. No significant influences were seen for patient age and sex, nor did the severity of dysplasia or the distinction between OLL and PVL affect outcome. On the other hand, both lesion appearance and site of origin, such that leukoplakia on the ventro-lateral tongue and floor of mouth were more likely to be DF post-laser, were significant influences (p=0.01 and p=0.04, respectively). Laser excision surgery was more effective than ablation techniques in achieving DF status (p=0.04).

Discussion

This paper has attempted a detailed review of the presentation and clinical outcome of 198 PMD patients diagnosed as OLL or PVL. Patients were identified from a previously reported cohort, which benefited from uniform diagnoses, consistent treatment intervention, long-term surveillance and documented clinical outcome[3,5,12].

Oral Lichenoid Lesions

Twenty percent of PMD lesions in this cohort were diagnosed as OLL; this is similar to previous reports suggesting that up to 29% of PMD may exhibit lichenoid features. Although OLL are classically described as solitary erythroleukoplakic lesions, mimicking the appearance of mucosal lichen planus, strict definition remains elusive[9]. Over 80% of OLL in this study appeared as leukoplakia, and were particularly common on ventro-lateral tongue, floor of mouth and labio-buccal mucosa sites; most were excised by laser surgery.

Upon microscopic examination, 72% of OLL in the study exhibited dysplasia most frequently mild or moderate in extent. Whilst the diagnostic term ‘lichenoid dysplasia’ has been proposed, raising specific concerns regarding long-term prognosis and increased MT risk, this terminology is not uniformly

supported in the literature[9,13,14]. It remains unclear whether LI drives MT, similar to chronic inflammation in the colonic cancer model, or is an immune response to atypical oral epithelium[1,9]; the latter hypothesis is favoured by the authors of this paper.

Whilst the prognostic significance of OLL has been debated for many years and is still controversial, there is increasing recognition in clinical practice that isolated OLL, especially those arising on the tongue, should be considered at high risk of MT and treated by interventional surgery[5,15]. Ultimately, OLL patients in this study were less likely to be DF post-treatment than those in the overall PMD cohort (69.5% vs 74.2%, respectively). MT following laser treatment affected 2 patients (1.7%), which is similar to the 1.09% to 2.1% range quoted in the literature[9,16].

It has not been common practice to continuously follow-up patients with OLL, although some authors now recommend this practice in specialist clinics to monitor for early cancerous change[7,8,15]. The findings of this study certainly support this approach.

Proliferative Verrucous Leukoplakia

PVL was diagnosed in 13.6% of the study cohort, much higher than the previously quoted prevalence of 0.1% in the UK population[17]. Lesions were predominantly leukoplakic in appearance (97.5%) with a high predilection for labio-buccal and gingival / alveolar sites (40%), and exhibiting more widespread mucosal involvement than OLL. A higher percentage of PVL (85%) showed dysplasia compared with OLL, although the majority were diagnosed as mild. Clinical outcomes were very similar to OLL, with DF status confirmed in 65% of patients and 2 (2.5%) progressing to OSCC, considerably better than previously reported 15% DF and 70% MT rates post-PVL treatment and strongly supportive of the efficacy of CO_2 laser as a treatment modality[3,20].

Traditionally, PVL diagnoses were made late during PMD presentation once spread to different sites, high recurrence following treatment and MT all

become apparent. Increasingly, specialist pathologists have attempted earlier and more objective diagnoses for verrucous hyperplastic lesions considered part of the PVL spectrum, probably explaining their increased diagnoses during the latter years of this study[3,17].

Salient criteria supporting PVL diagnoses have included: patients older than 60 years, a female: male ratio of 4:1, limited use of tobacco and alcohol, multiple-site disease and progressive clinical and histopathological features confirmed during follow-up[9,17]. Although PVL patients in this study were seen to be older, they displayed a more equal sex distribution, were active users of tobacco and alcohol, and were diagnosed as 'single-site' disease. It may be that these clinical presentations were at an early phase in PVL disease progression.

Diagnostic Discrepancy or Disease Evolution?

In 10 patients (5%) features of both OLL and PVL were identified, primarily in 'same-site' lesions at different time points. Whether this represents a discrepancy between incision and excision biopsy diagnoses, which is known to affect nearly 50% of PMD cases[3], or is representative of disease evolution remains unknown. Histopathologically, PVL is known to exhibit a continuum of morphological change, passing through an initial hyperkeratosis phase usually without dysplasia, through verrucous hyperplasia leading on to verrucous carcinoma and invasive OSCC[18]. Complicating the early phase of PVL are the presence of lymphocytic infiltrates in the immediate sub-epithelial region similar to OLL[9,19,20]. It is not an unreasonable hypothesis, therefore, that OLL and PVL may be part of the same PMD continuum.

Conclusions

Patient observational studies improve knowledge of PMD natural history. This paper reviewed the diagnosis and management of OLL and PVL. It was not a prospective or randomised trial and clinician bias may have influenced patient recruitment, treatment intervention and disease progression[3]; it is especially difficult for retrospective analysis to determine how much inherent

PMD behaviour or treatment contributes to clinical outcome[22,23]. Early intervention, especially laser excision surgery, is clearly an effective strategy with significantly improved DF status for treated patients. Whilst larger, multi-centre population studies are required, this study has demonstrated a continuum of clinico-pathological features for both OLL and PVL affecting one-third of PMD patients in North-East England. Whilst the OLL/PVL conundrum remains, clinicians specialising in PMD need to remain highly vigilant for signs and symptoms suggestive of this important PMD sub-group, liaising closely with pathology colleagues in agreeing diagnostic criteria appropriately tailored to individual, presenting cases.

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Competing Interests

None declared.

Ethical Approval

Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust Caldicott Guardian Approval for Anonymised Patient Data Collection & Retrospective Review of Hospital Records ID 4143 (2015).

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TABLE LEGEND

TABLE 1: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR ORAL LICHENOID LESION PATIENTS (n=118)

TABLE 2: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR PVL PATIENTS (n=80)

TABLE 3: STATISTICAL ANALYSES OF CLINICO-PATHOLOGICAL FEATURES THAT MIGHT INFLUENCE CLINICAL OUTCOME
(Pearson Chi-Square Testing)

TABLE 1: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR ORAL LICHENOID LESION PATIENTS (n=118)

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
1	1996/1	F	42	LK	Alveolus	HK + LI	Excision	Further
2	1998/1	M	60	ELK	Buccal	Severe Dysplasia + LI	Excision	Further
3	1998/2	M	66	LK	Buccal	Mild Dysplasia + LI	Excision	DF
4	1998/3	M	70	LK	FOM	Severe Dysplasia + LI	Excision	DF
5	1991/1	F	42	LK	FOM	Severe Dysplasia + LI	Excision	DF
6	1991/2	F	80	LK	Lateral Tongue	Severe Dysplasia + LI	Excision	DF
7	1999/3	M	53	LK	FOM	Moderate Dysplasia + LI	Excision	Further
8	2000/1	M	35	LK	FOM	Moderate Dysplasia + LI	Excision	DF
9	2000/2	F	59	LK	FOM	Moderate Dysplasia + LI	Excision	DF
10	2000/3	M	49	LK	FOM	Moderate Dysplasia + LI	Excision	DF
11	2000/4	F	67	LK	Buccal	Moderate Dysplasia + LI	Excision	DF
12	2000/5	F	40	LK	FOM	Moderate Dysplasia + LI	Excision	DF
13	2000/6	F	54	LK	Alveolus	Moderate Dysplasia + LI	Ablation	Further
14	2000/7	M	35	LK	FOM	Moderate Dysplasia + LI	Excision	DF
15	2000/8	M	27	ELK	FOM	Moderate Dysplasia + LI	Excision	DF
16	2000/9	M	65	LK	Ventral Tongue	Mild Dysplasia + LI	Excision	Further
17	2000/10	M	49	LK	Labial Comm	Severe Dysplasia + LI	Excision	Further
18	2001/1	M	48	LK	FOM	Moderate Dysplasia + LI	Excision	DF
19	2001/2	F	59	LK	Alveolus	Moderate Dysplasia + LI	Ablation	DF
20	2001/3	F	78	LK	Ventral Tongue	Moderate Dysplasia + LI	Excision	DF
21	2001/4	M	48	LK	FOM	Moderate Dysplasia + LI	Excision	DF
22	2001/5	M	65	ELK	Buccal	HK + LI	Excision	DF
23	2001/6	M	65	LK	Ventral Tongue	Moderate Dysplasia + LI	Excision	DF
24	2001/7	M	60	LK	FOM	Severe Dysplasia + LI	Excision	Further
25	2001/8	F	40	LK	FOM	Moderate Dysplasia + LI	Excision	DF
26	2002/1	M	27	LK	FOM	Moderate Dysplasia + LI	Excision	Further
27	2002/2	F	76	LK	Buccal	Moderate Dysplasia + LI	Excision	DF
28	2003/1	M	35	LK	FOM	Moderate Dysplasia + LI	Excision	DF

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
29	2003/2	F	73	ELK	Lateral Tongue	HK + LI	Excision	Further
30	2003/3	F	53	ELK	Buccal	Moderate Dysplasia + LI	Ablation	Further
31	2003/4	M	44	ELK	Lateral Tongue	Severe Dysplasia + LI	Excision	Further
32	2003/5	F	45	LK	Lateral Tongue	Mild Dysplasia + LI	Ablation	DF
33	2004/1	F	63	LK	FOM	Moderate Dysplasia + LI	Excision	DF
34	2004/2	F	68	LK	Lateral Tongue	HK + LI	Excision	MT
35	2004/3	M	73	LK	Lateral Tongue	Severe Dysplasia + LI	Excision	DF
36	2004/4	M	38	LK	FOM	Mild Dysplasia + LI	Excision	DF
37	2004/5	F	44	ELK	Labial Comm	Mild Dysplasia + LI	Excision	DF
38	2006/1	M	43	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
39	2006/2	M	84	LK	Ventral Tongue	Moderate Dysplasia + LI	Excision	DF
40	2006/3	M	40	LK	Palate	Moderate Dysplasia + LI	Excision	DF
41	2006/4	F	50	LK	FOM	Mild Dysplasia + LI	Excision	DF
42	2006/5	M	49	LK	Ventral Tongue	Mild Dysplasia + LI	Excision	DF
43	2007/1	F	64	ELK	Alveolus	HK + LI	Ablation	Further
44	2008/1	M	70	LK	FOM	Mild Dysplasia + LI	Excision	DF
45	2008/2	M	43	ELK	FOM	Mild Dysplasia + LI	Excision	Further
46	2008/3	F	51	LK	Buccal	HK + LI	Excision	DF
47	2008/4	M	70	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	MT
48	2008/5	F	69	LK	Buccal	HK + LI‡	Excision	Further
49	2008/6	F	65	ELK	Alveolus	HK + LI	Ablation	DF
50	2008/7	F	55	LK	FOM	Mild Dysplasia + LI	Excision	DF
51	2009/1	M	56	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
52	2009/2	M	48	LK	Ventral Tongue	Severe Dysplasia + LI	Excision	Further
53	2009/3	M	53	LK	Lateral Tongue	Moderate Dysplasia + LI	Excision	DF
54	2009/4	F	62	LK	Ventral Tongue	Moderate Dysplasia + LI	Excision	DF
55	2009/5	M	56	LK	FOM	Mild Dysplasia + LI	Excision	DF
56	2010/1	M	69	LK	FOM	Mild Dysplasia + LI	Excision	Further

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
57	2010/2	M	67	ELK	Lateral Tongue	Mild Dysplasia + LI	Excision	Further
58	2010/3	M	58	LK	Buccal	HK + LI	Excision	Further
59	2010/4	F	73	LK	Lateral Tongue	HK + LI	Excision	DF
60	2010/5	F	50	LK	Palate	HK + LI	Excision	DF
61	2010/6	M	72	LK	Alveolus	HK + LI*****	Excision	Further
62	2010/7	F	44	ELK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
63	2010/8	F	54	LK	Gingiva	HK + LI	Excision	DF
64	2010/9	M	60	LK	Lateral Tongue	Moderate Dysplasia + LI	Excision	DF
65	2010/10	F	48	LK	Ventral Tongue	Mild Dysplasia + LI	Excision	DF
66	2011/1	M	63	LK	Labial	Severe Dysplasia + LI	Ablation	Further
67	2011/2	M	57	LK	Palate	Moderate Dysplasia + LI	Excision	Further
68	2011/3	M	57	LK	FOM	Severe Dysplasia + LI	Excision	DF
69	2011/4	F	77	LK	Buccal	Mild Dysplasia + LI	Excision	Further
70	2011/5	F	72	LK	FOM	Mild Dysplasia + LI*	Excision	Further
71	2011/6	F	74	LK	Gingiva	HK + LI	Ablation	DF
72	2011/7	M	27	LK	FOM	Mild Dysplasia + LI	Excision	DF
73	2011/8	F	78	ELK	Buccal	HK + LI	Excision	DF
74	2011/9	F	49	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
75	2011/10	M	41	LK	FOM	Mild Dysplasia + LI	Excision	DF
76	2011/11	F	56	ELK	Lateral Tongue	Mild Dysplasia + LI	Excision	Further
77	2011/12	F	55	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
78	2011/13	F	65	LK	Gingiva	HK + LI	Ablation	DF
79	2011/14	M	49	ELK	Labial Comm	Mild Dysplasia + LI	Excision	Further
80	2011/15	F	57	LK	Gingiva	HK + LI	Ablation	Further
81	2012/1	M	62	LK	Labial Comm	HK + LI	Excision	DF
82	2012/2	M	51	LK	Buccal	HK + LI	Excision	Further
83	2012/3	M	73	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
84	2012/4	F	24	LK	FOM	Mild Dysplasia + LI	Excision	Further
85	2012/5	M	62	LK	Labial Comm	HK + LI	Excision	DF
86	2012/6	F	53	LK	Gingiva	HK + LI	Ablation	DF

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
87	2012/7	F	35	LK	Labial Comm	Mild Dysplasia + LI	Excision	DF
88	2012/8	M	67	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
89	2012/9	F	52	LK	Palate	Mild Dysplasia + LI	Excision	DF
90	2012/10	F	63	LK	Gingiva	HK + LI	Ablation	DF
91	2013/1	M	70	ELK	Buccal	Mild Dysplasia + LI	Excision	Further
92	2013/2	F	83	LK	Buccal	HK + LI	Excision	Further
93	2013/3	M	52	ELK	Buccal	HK + LI	Excision	DF
94	2013/4	F	41	LK	Buccal	HK + LI	Excision	DF
95	2013/5	M	42	LK	FOM	Mild Dysplasia + LI	Excision	DF
96	2013/6	F	63	LK	Alveolus	HK + LI	Ablation	Further
97	2013/7	F	66	LK	Ventral Tongue	Mild Dysplasia + LI	Excision	DF
98	2013/8	F	66	LK	Dorsum Tongue	Severe Dysplasia + LI	Excision	DF
99	2013/9	M	72	LK	Buccal	Severe Dysplasia + LI	Excision	DF
100	2013/10	F	60	LK	Alveolus	HK + LI	Ablation	Further
101	2013/11	M	76	LK	Ventral Tongue	Moderate Dysplasia + LI	Excision	DF
102	2013/12	F	60	LK	Buccal	Mild Dysplasia + LI	Excision	DF
103	2013/13	F	74	LK	Buccal	Mild Dysplasia + LI	Excision	DF
104	2013/14	F	79	LK	Buccal	HK + LI	Excision	DF
105	2013/15	F	52	LK	Lateral Tongue	Severe Dysplasia + LI	Excision	Further
106	2013/16	F	64	ELK	Buccal	HK + LI	Excision	DF
107	2013/17	F	60	LK	Alveolus	HK + LI	Excision	DF
108	2013/18	F	66	ELK	Lateral Tongue	Moderate Dysplasia + LI	Excision	DF
109	2013/19	F	61	LK	Alveolus	HK + LI	Excision	DF
110	2013/20	M	55	LK	Lateral Tongue	Mild Dysplasia + LI	Excision	DF
111	2013/21	F	50	LK	FOM	HK + LI	Excision	DF
112	2013/22	M	58	LK	Lateral Tongue	Severe Dysplasia + LI	Excision	DF
113	2013/23	M	59	LK	Lateral Tongue	Moderate Dysplasia + LI	Excision	Further
114	2014/1	F	43	LK	FOM	Mild Dysplasia + LI	Excision	DF
115	2014/2	M	65	LK	Labial Comm	Mild Dysplasia + LI	Excision	DF
116	2014/3	M	52	LK	Labial Comm	HK + LI	Excision	DF

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
117	2014/4	M	60	LK	Buccal	Mild Dysplasia + LI	Excision	DF
118	2014/5	F	53	LK	Lateral Tongue	Severe Dysplasia + LI	Excision	DF

*LK: leukoplakia; ELK: erythroleukoplakia; Labial Comm: Labial Commissure; FOM: floor of mouth; HK: hyperkeratosis; LI: lichenoid inflammation; DF: disease free; MT: malignant transformation; *PVL diagnosed on incision biopsy; ǂPVL identified in further disease*

TABLE 2: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR PVL PATIENTS (n=80)

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
1	2000/1	M	85	LK	Lateral Tongue	Moderate Dysplasia PVL	Ablation	DF
2	2000/2	M	82	LK	Buccal	Moderate Dysplasia PVL	Excision	DF
3	2002/1	F	61	LK	FOM	Moderate Dysplasia PVL	Excision	DF
4	2006/1	M	63	LK	Lateral Tongue	PVL	Excision	DF
5	2007/1	F	62	LK	Buccal	Mild Dysplasia PVL	Excision	Further
6	2007/2	F	33	LK	Dorsum Tongue	PVL	Excision	MT
7	2007/3	F	94	LK	Lateral Tongue	Mild Dysplasia PVL	Excision	DF
8	2008/1	F	72	LK	Labial	Moderate Dysplasia PVL	Ablation	MT
9	2008/2	F	62	LK	FOM	Mild Dysplasia PVL	Excision	DF
10	2009/1	F	60	LK	Lateral Tongue	Mild Dysplasia PVL	Excision	DF
11	2009/2	F	77	LK	Fauces	Severe Dysplasia PVL	Excision	DF
12	2009/3	F	54	LK	Lateral Tongue	PVL	Excision	DF
13	2010/1	F	77	LK	FOM	Moderate Dysplasia PVL	Excision	DF
14	2010/2	F	85	LK	Lateral Tongue	Mild Dysplasia PVL	Excision	DF
15	2010/3	M	69	LK	FOM	Mild Dysplasia PVL*****	Excision	Further
16	2010/4	M	58	LK	Buccal	PVL*****	Excision	Further
17	2010/5	F	74	LK	Buccal	Mild Dysplasia PVL	Excision	DF
18	2010/6	M	72	LK	Alveolus	PVL	Excision	Further
19	2010/7	F	53	LK	Dorsum Tongue	Mild Dysplasia PVL	Excision	DF
20	2010/8	F	71	LK	FOM	Severe Dysplasia PVL	Excision	DF
21	2010/9	M	70	LK	Buccal	Moderate Dysplasia PVL	Excision	Further
22	2010/10	M	79	LK	Alveolus	Mild Dysplasia PVL	Excision	Further
23	2010/11	F	36	LK	FOM	Mild Dysplasia PVL	Excision	DF
24	2011/1	F	77	LK	Buccal	Mild Dysplasia PVL**ǂ**	Excision	Further
25	2011/2	F	61	LK	Fauces	Moderate Dysplasia PVL	Excision	Further
26	2011/3	F	70	LK	Buccal	Moderate Dysplasia PVL	Excision	Further
27	2011/4	F	72	LK	FOM	Mild Dysplasia PVL	Excision	Further
28	2011/5	M	83	LK	Labial Comm	PVL	Excision	DF

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
29	2011/6	M	57	LK	Palate	Mild Dysplasia PVL	Excision	DF
30	2011/7	M	65	LK	Labial	Moderate Dysplasia PVL	Excision	DF
31	2011/8	F	64	LK	Lateral Tongue	Mild Dysplasia PVL	Excision	DF
32	2011/9	M	50	LK	Palate	Mild Dysplasia PVL	Ablation	DF
33	2011/10	M	38	LK	Buccal	Mild Dysplasia PVL	Excision	Further
34	2011/11	M	38	LK	Labial	Mild Dysplasia PVL	Excision	DF
35	2011/12	F	78	LK	Ventral Tongue	Severe Dysplasia PVL	Excision	DF
36	2011/13	M	67	LK	Fauces	Moderate Dysplasia PVL	Excision	DF
37	2011/14	M	63	LK	Buccal	Mild Dysplasia PVL	Excision	DF
38	2011/15	M	55	LK	Labial	Mild Dysplasia PVL	Excision	Further
39	2011/16	M	74	LK	Lateral Tongue	Mild Dysplasia PVL	Excision	Further
40	2011/17	M	46	ELK	Labial Comm	Severe Dysplasia PVL	Excision	Further
41	2011/18	F	58	LK	Gingiva	Mild Dysplasia PVL	Ablation	Further
42	2011/19	M	49	ELK	Labial Comm	Moderate Dysplasia PVL‡	Excision	Further
43	2012/1	M	62	LK	FOM	Moderate Dysplasia PVL	Excision	Further
44	2012/2	F	60	LK	FOM	Mild Dysplasia PVL	Excision	DF
45	2012/3	M	74	LK	Buccal	Moderate Dysplasia PVL	Excision	DF
46	2012/4	F	53	LK	FOM	Mild Dysplasia PVL	Excision	DF
47	2012/5	F	60	LK	Lateral Tongue	Moderate Dysplasia PVL	Excision	DF
48	2012/6	F	57	LK	Dorsum Tongue	Mild Dysplasia PVL	Excision	Further
49	2012/7	M	48	LK	FOM	Moderate Dysplasia PVL	Excision	DF
50	2012/8	M	40	LK	Labial Comm	Severe Dysplasia PVL	Excision	DF
51	2012/9	F	51	LK	Buccal	Mild Dysplasia PVL	Excision	Further
52	2012/10	M	74	LK	Palate	Moderate Dysplasia PVL	Excision	DF
53	2012/11	M	60	LK	Dorsum Tongue	Mild Dysplasia PVL	Excision	DF
54	2012/12	M	64	LK	Gingiva	PVL	Excision	Further
55	2012/13	F	71	LK	Buccal	Mild Dysplasia PVL	Ablation	Further
56	2012/14	M	64	LK	Palate	Mild Dysplasia PVL	Excision	DF
57	2012/15	F	25	LK	FOM	Mild Dysplasia PVL	Excision	DF

	Patient No	Sex	Age	Lesion	Site	Histopathology Diagnoses	Treatment	Outcome
58	2012/16	F	73	LK	Lateral Tongue	Moderate Dysplasia PVL	Excision	DF
59	2013/1	M	43	LK	Labial Comm	Mild Dysplasia PVL	Excision	DF
60	2013/2	M	36	LK	Labial Comm	Mild Dysplasia PVL	Excision	DF
61	2013/3	M	56	LK	Labial	PVL	Ablation	Further
62	2013/4	F	63	LK	Gingiva	PVL	Ablation	DF
63	2013/5	M	75	LK	Gingiva	Mild Dysplasia PVL	Ablation	Further
64	2013/6	F	56	LK	Lateral Tongue	Mild Dysplasia PVL	Excision	DF
65	2013/7	F	64	LK	Alveolus	PVL	Excision	DF
66	2013/8	M	45	LK	Ventral Tongue	Mild Dysplasia PVL	Excision	DF
67	2013/9	M	65	LK	Buccal	Mild Dysplasia PVL	Excision	DF
68	2013/10	F	71	LK	Buccal	Mild Dysplasia PVL	Excision	DF
69	2013/11	M	68	LK	Alveolus	PVL	Excision	Further
70	2013/12	F	66	LK	FOM	Mild Dysplasia PVL	Excision	DF
71	2013/13	M	37	LK	FOM	Moderate Dysplasia PVL	Excision	DF
72	2013/14	M	64	LK	Gingiva	PVL	Ablation	DF
73	2013/15	M	82	LK	Palate	Mild Dysplasia PVL	Ablation	Further
74	2014/1	F	65	LK	Alveolus	Mild Dysplasia PVL	Excision	DF
75	2014/2	F	53	LK	FOM	Mild Dysplasia PVL*****	Excision	Further
76	2014/3	F	64	LK	Alveolus	Mild Dysplasia PVL	Ablation	DF
77	2014/4	F	49	LK	Ventral Tongue	Mild Dysplasia PVL	Excision	DF
78	2014/5	M	69	LK	Ventral Tongue	Mild Dysplasia PVL*****	Excision	DF
79	2014/6	M	77	LK	Buccal	Mild Dysplasia PVL*****	Excision	DF
80	2014/7	M	59	LK	FOM	Mild Dysplasia PVL	Excision	DF

*LK: leukoplakia; ELK: erythroleukoplakia; Labial Comm: Labial Commissure; FOM: floor of mouth; PVL: proliferative verrucous leukoplakia; DF: disease free; MT: malignant transformation; *LI diagnosed on incision biopsy; ǂLI identified in further disease*

TABLE 3: STATISTICAL ANALYSES OF CLINICO-PATHOLOGICAL FEATURES THAT MIGHT INFLUENCE CLINICAL OUTCOME
(Pearson Chi-Square Testing)

	χ^2	p-value
Age[‡]	0.60	p=0.44
Sex	1.48	p=0.30
Lesion Appearance (Leukoplakia vs Others)	6.62	***p=0.01****
Lesion Site	12.11	***p=0.04****
Dysplasia Severity	2.64	p=0.43
OLL vs PVL	0.44	p=0.55
Treatment (Excision vs Ablation)	5.06	***p=0.04****

**Statistical Significance at α=0.05*

[‡]*Wald chi-square statistic & p-value computed by logistic regression*