# *Treatment Resistance in Potentially Malignant Disorders – 'Nature' or 'Nurture'…?*

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## Abstract

**Background:** Contemporary potentially malignant disorder management is based upon provisional histological diagnosis followed by interventional surgery to excise or ablate ‘high risk’ mucosal lesions. Although the majority of patients achieve disease free status post-treatment, others develop further or persistent disease unresponsive to intervention.

**Methods:** A detailed, retrospective clinico-pathological review of treatment resistant potentially malignant lesions, from a 590 patient cohort treated by $CO_2$ laser surgery and followed for a mean of 7.3 years, was undertaken. Clinical outcome was determined at study census date (31 December 2014).

**Results:** A total of 87 patients (15%) exhibited PMD disease resistant to treatment: 34 (6%) became disease free following further treatment, whilst 53 (9%) had persistent disease despite intervention. Disease free patients were younger, changed lesion appearance from erythroleukoplakia to leukoplakia ($p=0.004$), developed further lesions at new sites, demonstrated reduction in dysplasia severity with time, and required multiple treatments to achieve disease free status ($p=0.0005$). In contrast, persistent disease patients were older, male, often presented with proliferative verrucous leukoplakia on gingival and alveolar sites, displayed less severe dysplasia initially and underwent laser ablation rather than excision ($p=0.027$).

**Conclusion:** Despite clinico-pathological profiling of treatment resistant patients, the precise inter-relationship between the inherent nature of potentially malignant disease and the external influence of treatment intervention remains obscure.

## Introduction

Oral potentially malignant disorders (PMD), most frequently leukoplakia but also erythroplakia, erythroleukoplakia and proliferative verrucous leukoplakia (PVL), are distinct, clinically recognisable mucosal lesions known to precede invasive squamous cell carcinoma (SCC) development. Understanding of their natural history and risk of progression remains elusive in contemporary clinical practice[1,2]. PMDs are characterised by variable epithelial disorganisation and dysmaturation changes, identified microscopically as dysplasia, and subjectively graded for severity[1,2]. Systematic review has estimated an overall 12% risk of SCC development over a mean transformation time of 4.3 years, but with increased risk for erythroleukoplakia, lesions exhibiting more severe dysplasia and origin on ventro-lateral tongue and floor of mouth sites[3-5].

Whilst long-term observational studies of PMD patients have been advised to increase knowledge and identify reliable clinico-pathological predictors of disease outcome[6,7], PMD management is based upon incision biopsy for provisional histological assessment followed by surgical excision to provide definitive diagnoses and treatment of lesions deemed 'high-risk'[4,8].

It has been suggested, however, that PMD natural history may be independent of treatment intervention, and that a subgroup of lesions may be resistant to treatment and pre-destined for cancer development, although this seems a distinctly negative perspective[9].

We have previously documented clinical outcomes in a 590 PMD patient cohort undergoing standardised interventional $CO_2$ laser treatment, primarily excision surgery but also utilising ablation techniques for small or less dysplastic lesions on gingival and alveolar sites[6]. Post-treatment, 404 patients from this cohort (68.4%) were found to be disease free, 99 (16.8%) exhibited unexpected or subsequently developing SCC, whilst 87 were resistant to treatment developing further or persistent PMD disease during the mean 7.3 years follow-up period[4,5].

The specific purpose of this paper, therefore, was to review in depth the clinico-pathological features of these 87 ‘treatment resistant’ PMDs, to document each individual patient ‘journey’ and try to improve knowledge of the natural history of PMD disease and thereby identify features potentially predictive of poor outcome post-treatment.

## Method

Caldicott Approval 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 required new patients who presented with single-site disease resistant to initial treatment intervention. Recorded demographic and clinico-pathological data included: patient age and sex, appearance and site of presenting PMD, histopathology diagnoses, date, number and type of treatment interventions (laser excision or ablation), appearance and site of further or persistent PMD, and clinical outcome at the study census date (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[4]. 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[4]. The World Health Organization (WHO) system was used and dysplasia classified as mild, moderate and severe or carcinoma-in-situ (CiS). Diagnoses of hyperkeratosis (HK), lichenoid inflammation (LI), PVL and chronic hyperplastic candidosis (CHC) were made as appropriate.

Clinical outcomes were defined as: disease free or persistent disease, and distinguished between same-site and/or multi-focal PMD development.

### 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) were used to assess the association between PMD clinico-pathological features and post-treatment clinical outcome (disease free / persistent disease). All statistical analyses were carried out using the R Environment for Statistical Computing (version 3.2.5).

## Results

Two distinct groups of treatment resistant PMD were identified: 34 patients who achieved disease free status following further intervention, and 53 who exhibited persistent PMD at study census despite treatment. All patients were noted to be tobacco smokers and regularly consumed alcohol.

### *Disease Free Patients*

Data for the 34 disease free patients are listed in Table 1 which summarises individual patient 'journeys' from initial presentation to disease free status; there were 18 males and 16 females (age range 43-83yrs; mean 57.7yrs).

*Clinical Appearance*. Presenting PMD appearance included 25 leukoplakias (74%), 8 erythroleukoplakias (23%) and 1 erythroplakia (3%). In 23 cases (68%), further PMD disease exhibited consistent clinical features, whilst 11 (32%) changed appearance, in 8 (23%) initially presenting eryrtholeukoplakia transformed into a subsequent leukoplakia.

*Site*. 16 lesions (47%) arose on the ventro-lateral tongue and floor of mouth, 9 (26%) were seen on the buccal mucosa but other oral sites were less frequently involved. 15 further lesions (44%) arose specifically at the same-site as their previous PMD, whilst 19 patients (56%) developed same and new-site (multi-focal) disease.

*Histopathology*. 28 initially presenting lesions (82%) were dysplastic on histopathological examination, with severe dysplasia or CiS seen in 15 (44%); PVL was identified in 5 (15%), lichenoid inflammation in 5 (15%) and CHC in 2 (6%). 43 further PMD lesions were identified in this group over the study period: 13 patients (38%) exhibited the same histological features in both initial and further lesions, whilst 16 (47%) developed less severe and 5 (15%) more severe pathological change, before ultimately reaching disease free status.

*Treatment.* In total, 77 interventions were performed in the 34 patients: 61 laser excisions (79%) and 16 (21%) ablative procedures. All patients underwent multiple interventions, with individual patient treatments ranging from 2 to 4 (mean 2.26). Time between first and last treatments varied between 4 and 129 months, with a mean of 33.1 months.

***Persistent Disease Patients***

Table 2 summarises the clinical course and disease outcome status for 53 patients exhibiting persistent PMD disease: 31 males and 22 females (age range 24-93yrs; mean 61yrs).

*Clinical Appearance.* 45 initial lesions appeared as leukoplakia (85%), 6 as erythroleukoplakia (11%) and 2 erythroplakia (4%); 45 (85%) retained consistent appearance whilst 8 (15%) changed appearance, with 5 (9%) erythroleukoplakic lesions transforming to leukoplakia.

*Site*. Initial site involvement included 17 (32%) arising on ventro-lateral tongue and floor of mouth, 14 (26%) on buccal mucosa and 11 (21%) on gingiva / alveolar mucosa, with other sites involved less frequently. 28 subsequent lesions (53%) were identified at the same site as presenting disease, whilst 25 (47%) exhibited same and new-site (multi-focal) lesions.

*Histopathology*. 39 initial lesions (74%) exhibited dysplasia on biopsy, with 29 mild or moderate dysplasia (55%) and only 12 (23%) showing severe dysplasia or CiS. PVL was initially seen in 20 cases (38%) and lichenoid inflammation in 9 (17%); no CHC cases were identified. Comparative histopathology data were only available for 17 cases undergoing further

biopsy: 5 (29%) showed similar pathological features with 7 (42%) less severe and 5 (29%) more severe than original biopsies.

*Treatment.* 78 treatment interventions were recorded in this group, with 49 excisions (63%) and 29 (37%) laser ablations. Only 15 patients underwent multiple interventions with the number per patient ranging between 1 and 4 (mean 1.47); the time between first and final intervention for these cases ranged from 6 to 82 months (mean 35.53 months).

### *Statistical Comparison*

Table 3 summarises statistical comparisons between disease free and persistent patient groups. No significant differences were seen for patient age and sex, nor for individual PMD lesion clinical appearance, site or histopathology diagnoses, including PVL or LI recognition. Statistical significance was identified, however, for a change in PMD appearance between initial and subsequent lesions ($p=0.004$) and for treatment intervention, both in terms of multiple versus single treatment ($p=0.0005$) and the use of excision rather than ablation techniques ($p=0.027$).

## Discussion

The efficacy of interventional laser surgery, as both a diagnostic and treatment tool, has been well documented[10]. Recognition that 70% of 'high-risk' PMD patients can achieve disease free status by intervention is unquestionably a treatment success[4,8]. It is, however, the subgroup of PMD patients who respond poorly to treatment that are likely to provide new and salient information regarding the nature of persistent and aggressive PMD disease[4].

Treatment resistance may be defined as PMD which persists or recurs, either at same or new-site origin, following interventional management. In the absence of relevant, prospective randomised trials, comparative studies of outcome in treated patient cohorts provide best contemporaneous evidence to detail PMD natural history and progression[6,8]. In view of the inability of

currently available biomarkers to rationalise clinical management decisions, in-depth study of observed patient outcomes may help validate clinico-pathological predictors of PMD behaviour[1,8].

This paper attempted a detailed review of the natural history of 87 patients with treatment resistant PMD. Patients were identified from a previously reported cohort, which benefited from uniform diagnostic techniques, consistent treatment intervention and long-term observation of clinical outcome[4,8]. Accepting inevitable limitations of a single-centre, retrospective study, it was nonetheless possible to delineate two distinct types of treatment resistance: patients who ultimately achieved disease free status following further treatment and those with persistent PMD despite intervention.

***Clinico-Pathological Profiling***

Whilst the relatively small patient numbers in the analysis undoubtedly influenced statistical significance, it remains pertinent to characterise the clinico-pathological profiles of the two subgroups because such features may predict outcome and guide patient management decisions in the future.

Disease free patients were slightly younger, often had lesions that changed appearance from erythroleukoplakia to ‘lower risk’ leukoplakia, developed further PMDs at new sites and, whilst often exhibiting quite severe dysplasia in presenting lesions, generally showed a reduction in severity in subsequent lesions.

In contrast, the persistent disease cohort were generally older, more often male, frequently exhibited leukoplakia with PVL features at gingival and alveolar sites, and displayed less severe dysplasia in initial biopsies. Clinical appearance of lesions was more consistent between initial and further presentation, and same-site disease more prevalent.

Diagnoses of PVL, with or without dysplasia, were made more frequently during later years of the study (2007 onwards), probably due to enhanced awareness amongst pathologists of the risks for persistent PMD disease and increased malignant transformation in PVL[11]. Although the identification of LI within PMD lesions has been linked to persistent and unfavourable disease

outcome[12], no significant influence was seen on treatment resistance in this investigation.

***The Patient 'Journey'***

Active patient surveillance post-intervention is advised, not only to review treatment efficacy but also to effectively monitor patients for further disease, to recognise early signs of malignancy and to improve understanding of PMD natural history[8,14]. Table 1 details the cyclical nature of successful intervention for 34 disease free cases, passing from surgery to surveillance to repeat surgery on recognition of further disease, often taking several years and multiple treatments[8,14]; $CO_2$ laser surgery has the advantage of facilitating repeat intervention without compromising oral form or function[10,14]. Despite consistent management decisions and repeated treatment, the 53 patient 'journeys' summarized in Table 2 led to persistent disease outcomes.

***Treatment Intervention***

Whilst all PMD treatments were coordinated by the first author (PJT) and proceeded along well-established and consistent management guidelines[4,8,10], it is clear that fewer interventions per patient were performed in the persistent disease group. Although many of these treatments comprised laser ablation of gingival and alveolar PVL, as previously advocated for this type of presentation[8,12], repeat excision surgeries for more significant dysplastic lesions were also carried out, obviously with reduced efficacy compared to disease free cases.

Whilst it is likely that individual management decisions and choice of treatment modality influence PMD clinical outcome[15,16], it remains unclear from this retrospective study whether the inherent nature of the presenting PMD disease or the treatment intervention itself contributes the principal determinant of clinical outcome. Most probably, clinical outcome is the result of a complex interaction between 'nature' and 'nurture'.

It is, however, notable that repeat excision surgeries were performed much more frequently in patients achieving disease free status than those with persistent disease. Is the answer to PMD treatment resistance, therefore,

more treatment? Undoubtedly, future multi-centre, prospective investigations will be required to characterise this issue further.

***Clinical Relevance of Treatment Resistant PMD***

Despite recognising and defining salient clinico-pathological characteristics of treatment resistant PMD, an important question remains regarding the precise clinical relevance of persistent PMD. The hypothesis is clear: PMD treatment resistance reflects more aggressive disease and an enhanced cancer risk. Current evidence, however, is not wholly supportive of this concept, because none of the 87 treatment resistant patients in this analysis developed SCC. On the contrary, the majority of SCCs identified in the 590 cohort were pre-existing and diagnosed unexpectedly upon initial PMD lesion excision[4].

Patient observational studies provide invaluable insight into the natural history of PMD, but it is evident that new approaches to clinico-pathological and biomolecular profiling are urgently needed to characterise disease progression in large population-based investigations. Only in this way will we truly enhance our knowledge and understanding of oral carcinogenesis and improve prognoses for patients.

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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 1: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR DISEASE FREE PATIENTS (n=34)**

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Further PMD | No of Interventions |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 1997/6 | M | 47 | Aug 1997 | LK | FOM | CiS | Excision | | |
| | | | | May 2000 | LK | FOM | Severe Dysplasia | Excision | Same | 2 |
| **2** | 1998/12 | M | 60 | Nov 1998 | ELK | Buccal | Severe Dysplasia+LI | Excision | | |
| | | | | Jun 2005 | LK | Buccal | Mild Dysplasia | Excision | Same | 2 |
| **3** | 1999/9 | M | 53 | May 1999 | LK | FOM | CiS | Excision | | |
| | | | | Jun 2000 | LK | FOM | Severe Dysplasia | Excision | | |
| | | | | Sept 2001 | LK | Lateral Tongue | Severe Dysplasia | Excision | Same + New | 3 |
| **4** | 2001/5 | F | 58 | Feb 2001 | LK | Buccal | Moderate Dysplasia | Excision | | |
| | | | | July 2002 | LK | Alveolus | Moderate Dysplasia+LI | Ablation | New | 2 |
| **5** | 2001/12 | M | 60 | Jun 2001 | LK | FOM | Severe Dysplasia | Excision | | |
| | | | | July 2003 | LK | Ventral Tongue | Moderate Dysplasia | Excision | | |
| | | | | Dec 2004 | LK | Lateral Tongue | Moderate Dysplasia | Excision | New | 3 |
| **6** | 2002/9 | F | 64 | Oct 2002 | ELK | FOM | CiS | Excision | | |
| | | | | July 2004 | LK | Fauces | Severe Dysplasia | Excision | New | 2 |
| **7** | 2002/16 | M | 45 | Dec 2002 | LK | Gingiva | Mild Dysplasia | Ablation | | |
| | | | | Sept 2013 | LK | Labial | Mild Dysplasia | Ablation | New | 2 |
| **8** | 2004/18 | F | 55 | July 2004 | LK | Palate | Severe Dysplasia | Ablation | | |
| | | | | Feb 2005 | LK | Fauces | CiS | Excision | New | 2 |
| **9** | 2004/23 | M | 49 | Oct 2004 | LK | Lateral Tongue | CiS | Excision | | |

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Further PMD | No of Interventions |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Feb 2005 | LK | Lateral Tongue | CiS | Excision | | |
| | | | | Aug 2012 | ELK | Lateral Tongue | Mild Dysplasia | Excision | New | 3 |
| **10** | 2006/6 | M | 83 | Mar 2006 | LK | Lateral Tongue | Severe Dysplasia | Excision | | |
| | | | | Jun 2007 | LK | Ventral Tongue | Moderate Dysplasia | Excision | New | 2 |
| **11** | 2006/7 | F | 67 | Jun 2006 | LK | Lateral Tongue | Moderate Dysplasia | Excision | | |
| | | | | Sept 2007 | LK | Lateral Tongue | Mild Dysplasia | Excision | Same | 2 |
| **12** | 2007/26 | F | 61 | Nov 2007 | LK | Buccal | Severe Dysplasia | Excision | | |
| | | | | Mar 2011 | ELK | Alveolus | HK + LI | Ablation | | |
| | | | | Mar 2012 | EK | Alveolus | Moderate Dysplasia | Ablation | Same + New | 3 |
| **13** | 2008/3 | M | 43 | Feb 2008 | ELK | FOM | Mild Dysplasia | Excision | | |
| | | | | June 2014 | LK | FOM | Mild Dysplasia | Ablation | Same | 2 |
| **14** | 2009/14 | M | 48 | Mar 2009 | LK | Ventral Tongue | Severe Dysplasia | Excision | | |
| | | | | Apr 2010 | LK | FOM | Severe Dysplasia+LI | Excision | New | 2 |
| **15** | 2009/23 | F | 44 | Jul 2009 | ELK | Dorsum Tongue | CHC | Excision | | |
| | | | | Jun 2014 | LK | Dorsum Tongue | CHC | Excision | Same | 2 |
| **16** | 2009/33 | F | 63 | Oct 2009 | ELK | Lateral Tongue | Severe Dysplasia | Excision | | |
| | | | | Oct 2011 | ELK | Lateral Tongue | Severe Dysplasia | Ablation | | |
| | | | | July 2012 | LK | Ventral Tongue | Mild Dysplasia | Ablation | Same + New | 3 |
| **17** | 2009/40 | M | 68 | Nov 2009 | ELK | FOM | CiS | Excision | | |
| | | | | July 2011 | LK | FOM | CiS | Ablation | | |
| | | | | May 2013 | LK | FOM | Severe Dysplasia | Excision | | |

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Further PMD | No of Interventions |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Sept 2014 | LK | Ventral Tongue | Severe Dysplasia | Excision | Same + New | 4 |
| **18** | 2010/10 | M | 58 | Mar 2010 | LK | Buccal | PVL | Excision | | |
| | | | | Oct 2010 | LK | Labial Comm | PVL | Excision | New | 2 |
| **19** | 2011/3 | M | 57 | Jan 2011 | LK | Palate | Moderate Dysplasia+LI | Excision | | |
| | | | | May 2012 | LK | Palate | Moderate Dysplasia | Excision | Same | 2 |
| **20** | 2011/9 | F | 77 | Feb 2011 | LK | Buccal | Mild Dysplasia PVL | Excision | | |
| | | | | Jun 2013 | LK | Buccal | Mild Dysplasia+LI | Excision | Same | 2 |
| **21** | 2011/17 | F | 72 | Mar 2011 | LK | FOM | Mild Dysplasia PVL | Excision | | |
| | | | | Jun 2013 | LK | Buccal | Mild Dysplasia+LI | Excision | New | 2 |
| **22** | 2011/24 | M | 65 | May 2011 | LK | Palate | Severe Dysplasia | Excision | | |
| | | | | Nov 2012 | LK | Lateral Tongue | Moderate Dysplasia | Excision | | |
| | | | | Nov 2014 | ELK | RM | Severe Dysplasia | Excision | New | 3 |
| **23** | 2011/27 | F | 45 | May 2011 | LK | Palate | Mild Dysplasia | Excision | | |
| | | | | Mar 2014 | LK | Palate | Mild Dysplasia | Ablation | Same | 2 |
| **24** | 2011/34 | M | 47 | Jun 2011 | LK | Labial Comm | CHC | Excision | | |
| | | | | Jun 2013 | LK | Labial Comm | CHC | Ablation | Same | 2 |
| **25** | 2011/50 | M | 74 | Sept 2011 | LK | Lateral Tongue | Mild Dysplasia PVL | Excision | | |
| | | | | July 2012 | LK | Buccal | Mild Dysplasia | Excision | New | 2 |
| **26** | 2011/51 | M | 46 | Sept 2011 | ELK | Labial Comm | Mild Dysplasia PVL | Excision | | |
| | | | | Dec 2013 | LK | Ventral Tongue | Severe Dysplasia | Excision | | |
| | | | | Dec 2014 | LK | Labial Comm | Mild Dysplasia PVL | Ablation | Same + New | 3 |

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Further PMD | No of Interventions |
|---|---|---|---|---|---|---|---|---|---|---|
| **27** | 2011/62 | F | 57 | Dec 2011 | LK | Gingiva | HK + LI | Ablation | | |
| | | | | Jun 2014 | LK | Gingiva | HK + LI | Ablation | Same | 2 |
| **28** | 2012/24 | F | 51 | Jun 2012 | LK | Buccal | PVL | Excision | | |
| | | | | May 2013 | LK | Buccal | Mild Dysplasia PVL | Excision | Same | 2 |
| **29** | 2013/1 | M | 70 | Jan 2013 | ELK | Buccal | Mild Dysplasia+LI | Excision | | |
| | | | | May 2013 | ELK | Buccal | HK + LI | Excision | Same | 2 |
| **30** | 2013/5 | M | 54 | Jan 2013 | EK | Fauces | Severe Dysplasia | Excision | | |
| | | | | Feb 2014 | LK | Fauces | Severe Dysplasia | Excision | Same | 2 |
| **31** | 2013/30 | F | 60 | May 2013 | LK | Alveolus | HK + LI | Ablation | | |
| | | | | Jun 2014 | LK | FOM | Mild Dysplasia | Excision | New | 2 |
| **32** | 2013/34 | M | 47 | May 2013 | LK | FOM | Mild Dysplasia | Excision | | |
| | | | | May 2014 | LK | FOM | Mild Dysplasia | Excision | Same | 2 |
| **33** | 2013/42 | F | 52 | Jun 2013 | LK | Lateral Tongue | Severe Dysplasia | Excision | | |
| | | | | May 2014 | LK | Lateral Tongue | Severe Dysplasia | Excision | Same | 2 |
| **34** | 2013/54 | F | 63 | Aug 2013 | LK | FOM | Mild Dysplasia | Excision | | |
| | | | | Jun 2014 | LK | Palate | Mild Dysplasia | Excision | New | 2 |

*LK: leukoplakia; ELK: erythroleukoplakia; EK: erythroplakia; Labial Comm: Labial Commissure; FOM: floor of mouth; RM: retromolar region; PVL: proliferative verrucous leukoplakia; HK: hyperkeratosis; LI: lichenoid inflammation; CHC: chronic hyperplastic candidosis; CiS: carcinoma-in-situ*

**TABLE 2: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR PERSISTENT DISEASE PATIENTS (n=53)**

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Persistent PMD | No of Interventions | Clinical Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 2000/12 | F | 54 | March 2000 | LK | Alveolus | Moderate Dysplasia+LI | Ablation | Same + New | 1 | MF LK |
| **2** | 2000/33 | M | 59 | Oct 2000 | LK | Ventral Tongue | Moderate Dysplasia | Excision | | | |
| | | | | Nov 2006 | LK | Ventral Tongue | Mild Dysplasia | Excision | Same | 2 | Ventral Tongue LK |
| **3** | 2001/13 | M | 55 | July 2001 | ELK | Fauces | CiS | Excision | Same + New | 1 | MF LK |
| **4** | 2001/16 | F | 65 | Sept 2001 | LK | Gingiva | Mild Dysplasia | Ablation | Same | 1 | Gingiva LK |
| **5** | 2002/8 | M | 41 | June 2002 | LK | FOM | CiS | Excision | | | |
| | | | | June 2004 | ELK | FOM | Moderate Dysplasia | Ablation | | | |
| | | | | May 2005 | LK | Ventral Tongue | Severe Dysplasia | Excision | | | |
| | | | | May 2007 | ELK | Lateral Tongue | Severe Dysplasia | Excision | New | 4 | MF ELK |
| **6** | 2002/10 | M | 27 | Oct 2002 | LK | FOM | Moderate Dysplasia+LI | Excision | Same | 1 | FOM LK |
| **7** | 2003/6 | F | 67 | Apr 2003 | EK | Buccal | Severe Dysplasia | Excision | | | |
| | | | | Feb 2010 | EK | Lateral Tongue | Severe Dysplasia | Excision | New | 2 | MF ELK |
| **8** | 2005/2 | M | 69 | Jan 2005 | LK | FOM | Moderate Dysplasia | Excision | Same | 1 | FOM LK |
| **9** | 2005/4 | M | 55 | Feb 2005 | LK | Lateral Tongue | CiS | Excision | | | |
| | | | | Mar 2006 | LK | FOM | Mild Dysplasia | Observation | New | 1 | FOM LK |
| **10** | 2006/11 | M | 56 | Aug 2006 | LK | FOM | Severe Dysplasia | Excision | | | |
| | | | | Oct 2010 | ELK | FOM | Severe Dysplasia | Excision | Same | 2 | FOM ELK |
| **11** | 2006/17 | F | 93 | Nov 2006 | EK | Buccal | Severe Dysplasia | Excision | Same | 1 | MF LK |
| **12** | 2007/7 | F | 58 | Mar 2007 | LK | FOM | Mild Dysplasia | Ablation | | | |

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Persistent PMD | No of Interventions | Clinical Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Mar 2009 | LK | Alveolus | Mild Dysplasia | Ablation | | | |
| | | | | Oct 2014 | LK | Buccal | Mild Dysplasia PVL | Ablation | New | 3 | MF LK |
| **13** | 2008/11 | M | 56 | Mar 2008 | LK | Lateral Tongue | Severe Dysplasia | Excision | | | |
| | | | | Mar 2009 | LK | Lateral Tongue | Moderate Dysplasia | Excision | Same | 2 | Lateral Tongue LK |
| **14** | 2008/28 | F | 67 | Sept 2008 | LK | Palate | Mild Dysp | Excision | | | |
| | | | | Feb 2010 | LK | Buccal | HK + LI | Excision | | | |
| | | | | Oct 2012 | LK | Alveolus | Mild Dysplasia PVL | Ablation | New | 3 | MF LK |
| **15** | 2009/10 | M | 52 | Feb 2009 | LK | Labial Comm | Mild Dysplasia | Excision | Same | 1 | Labial Comm LK |
| **16** | 2010/6 | M | 69 | Mar 2010 | LK | FOM | Mild Dysplasia PVL | Excision | New | 1 | Buccal LK |
| **17** | 2010/8 | M | 67 | Mar 2010 | ELK | Lateral Tongue | Mild Dysplasia+LI | Excision | Same | 1 | Lateral Tongue ELK |
| **18** | 2010/19 | M | 72 | June 2010 | LK | Alveolus | PVL | Excision | New | 1 | MF LK |
| **19** | 2010/28 | F | 56 | Sept 2010 | ELK | Labial Comm | Moderate Dysplasia | Excision | New | 1 | MF LK |
| **20** | 2010/30 | M | 70 | Sept 2010 | LK | Buccal | Moderate Dysplasia PVL | Excision | | | |
| | | | | Sept 2011 | LK | RM | Moderate Dysplasia | Ablation | New | 2 | MF LK |
| **21** | 2010/34 | F | 59 | Oct 2010 | LK | Palate | HK | Ablation | Same | 1 | Palate LK |
| **22** | 2010/39 | M | 79 | Dec 2010 | LK | Alveolus | Mild Dysplasia PVL | Excision | | | |
| | | | | Oct 2013 | LK | Palate | PVL | Ablation | | | |
| | | | | Oct 2014 | LK | Alveolus | Mild Dysplasia PVL | Ablation | New | 3 | MF LK |
| **23** | 2011/1 | M | 63 | Jan 2011 | LK | Labial | Severe Dysplasia+LI | Ablation | Same | 1 | Labial ELK |
| **24** | 2011/11 | F | 61 | Feb 2011 | LK | Fauces | Moderate Dysplasia PVL | Excision | New | 1 | MF LK |
| **25** | 2011/12 | F | 70 | Feb 2011 | LK | Buccal | Moderate Dysplasia PVL | Excision | New | 1 | MF LK |

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Persistent PMD | No of Interventions | Clinical Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **26** | 2011/22 | M | 42 | Mar 2011 | LK | Labial | Mild Dysplasia | Ablation | | | |
| | | | | Nov 2012 | LK | Labial | Mild Dysplasia | Ablation | Same | 2 | Labial LK |
| **27** | 2011/38 | M | 38 | July 2011 | LK | Buccal | Mild Dysplasia PVL | Excision | Same | 1 | Buccal LK |
| **28** | 2011/48 | F | 56 | Sept 2011 | ELK | Lateral Tongue | Moderate Dysplasia | Excision | | | |
| | | | | May 2012 | ELK | Buccal | Mild Dysplasia+LI | Excision | | | |
| | | | | June 2014 | LK | Lateral Tongue | Mild Dysplasia+LI | Excision | New | 3 | Lateral Tongue LK |
| **29** | 2011/49 | M | 55 | Sept 2011 | LK | Labial | Mild Dysplasia PVL | Excision | New | 1 | MF LK |
| **30** | 2011/58 | F | 58 | Nov 2011 | LK | Gingiva | Mild Dysplasia PVL | Ablation | Same | 1 | Gingiva LK |
| **31** | 2011/60 | M | 49 | Dec 2011 | ELK | Labial Comm | Mild Dysplasia PVL | Excision | | | |
| | | | | Mar 2013 | LK | Labial Comm | PVL | Ablation | | | |
| | | | | July 2013 | LK | Ventral Tongue | Moderate Dysplasia+LI | Excision | New | 3 | Labial Comm LK |
| **32** | 2011/61 | M | 68 | Dec 2011 | LK | Alveolus | Mild Dysplasia | Ablation | Same | 1 | Alveolus LK |
| **33** | 2012/2 | F | 62 | Jan 2012 | LK | FOM | Moderate Dysplasia PVL | Excision | | | |
| | | | | Jan 2013 | LK | FOM | Mild Dysplasia PVL | Ablation | | | |
| | | | | May 2013 | LK | FOM | Mild Dysplasia PVL | Ablation | Same | 3 | FOM LK |
| **34** | 2012/3 | M | 51 | Jan 2012 | LK | Buccal | HK + LI | Excision | Same | 1 | Buccal LK |
| **35** | 2012/5 | M | 80 | Jan 2012 | LK | Buccal | Moderate Dysplasia | Ablation | New | 1 | MF LK |
| **36** | 2012/15 | F | 24 | Apr 2012 | LK | FOM | Mild Dysplasia+LI | Excision | Same | 1 | FOM LK |
| **37** | 2012/18 | F | 57 | May 2012 | LK | Dorsum Tongue | Mild Dysplasia PVL | Excision | Same + New | 1 | MF LK |
| **38** | 2012/20 | F | 56 | May 2012 | ELK | Lateral Tongue | Severe Dysplasia | Excision | Same | 1 | Lateral Tongue LK |
| **39** | 2012/39 | M | 64 | Aug 2012 | LK | Gingiva | PVL | Excision | New | 1 | MF LK |

| | Patient No | Sex | Age | Date | Lesion | Site | Histopathology Diagnoses | Treatment | Site of Persistent PMD | No of Interventions | Clinical Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **40** | 2012/40 | M | 58 | Sept 2012 | LK | Ventral Tongue | Moderate Dysplasia | Excision | Same + New | 1 | MF LK |
| **41** | 2012/41 | F | 71 | Oct 2012 | LK | Buccal | Mild Dysplasia PVL | Ablation | New | 1 | MF LK |
| **42** | 2012/48 | M | 59 | Dec 2012 | LK | Ventral Tongue | Severe Dysplasia | Excision | Same | 1 | Ventral Tongue LK |
| **43** | 2013/3 | F | 83 | Jan 2013 | LK | Buccal | HK + LI | Excision | Same + New | 1 | MF LK |
| **44** | 2013/6 | M | 56 | Jan 2013 | LK | Labial | PVL | Ablation | Same + New | 1 | MF LK |
| **45** | 2013/15 | M | 75 | Mar 2013 | LK | Gingiva | PVL | Ablation | | | |
| | | | | Feb 2014 | LK | Gingiva | Mild Dysplasia PVL | Ablation | Same | 2 | Gingiva LK |
| **46** | 2013/19 | F | 63 | Mar 2013 | LK | Alveolus | HK + LI | Ablation | Same | 1 | Alveolus LK |
| **47** | 2013/47 | M | 68 | Jun 2013 | LK | Alveolus | PVL | Excision | Same | 1 | Alveolus LK |
| **48** | 2013/69 | M | 82 | Oct 2013 | LK | Palate | PVL | Ablation | | | |
| | | | | Oct 2014 | LK | Alveolus | Mild Dysplasia PVL | Ablation | Same + New | 2 | MF LK |
| **49** | 2013/71 | M | 59 | Nov 2013 | LK | Lateral Tongue | Moderate Dysplasia+LI | Excision | Same + New | 1 | MF LK |
| **50** | 2013/72 | F | 73 | Dec 2013 | LK | Labial | Severe Dysplasia | Excision | Same | 1 | Labial LK |
| **51** | 2014/14 | F | 53 | May 2014 | LK | FOM | Mild Dysplasia PVL | Excision | | | |
| | | | | Nov 2014 | LK | Gingiva | Mild Dysplasia PVL | Ablation | New | 2 | MF LK |
| **52** | 2014/19 | F | 65 | June 2014 | LK | Gingiva | PVL | Ablation | Same | 1 | Gingiva LK |
| **53** | 2014/25 | M | 63 | Sept 2014 | LK | Buccal | Severe Dysplasia | Excision | Same + New | 1 | MF LK |

*LK: leukoplakia; ELK: erythroleukoplakia; EK: erythroplakia; Labial Comm: Labial Commissure; FOM: floor of mouth; RM: retromolar region; MF: multi-focal; PVL: proliferative verrucous leukoplakia; HK: hyperkeratosis; LI: lichenoid inflammation; CHC: chronic hyperplastic candidosis; CiS: carcinoma-in-situ*

**TABLE 3: STATISTICAL COMPARISON OF CLINICO-PATHOLOGICAL FEATURES BETWEEN DISEASE FREE AND PERSISTENT DISEASE PATIENT GROUPS (Pearson Chi-Square Testing)**

| | $\chi^2$ | p-value |
|---|---|---|
| **Age** | 1.293 | p=0.28 |
| **Sex** | 0.259 | p=0.67 |
| **Initial Lesion Appearance** | 2.293 | p=0.35 |
| **Initial Lesion Site** | 7.659 | p=0.36 |
| **Initial Histopathology Diagnosis** | 5.816 | p=0.12 |
| **PVL in Initial Lesion** | 3.949 | p=0.09 |
| **Lichenoid Inflammation in Initial Lesion** | 0.021 | p=1.0 |
| **Treatment Intervention (Single vs Multiple)** | 43.282 | *p=0.0005** |
| **Treatment Intervention (Excision vs Ablation)** | 5.058 | *p=0.027** |
| **Time (months) between Initial and Final Intervention** | 0.157 | p=0.76 |
| **Change in Lesion Appearance** | 8.971 | *p=0.004** |
| **Change in Lesion Site (Same vs Multi-Focal)** | 0.077 | p=0.83 |
| **Change in Histopathology Diagnosis** | 1.587 | p=0.51 |

**Statistical Significance at α=0.05*