# Dysplastic Lesions of the Oral Cavity: A Clinical Care Conundrum Put Down that Knife…(for now)

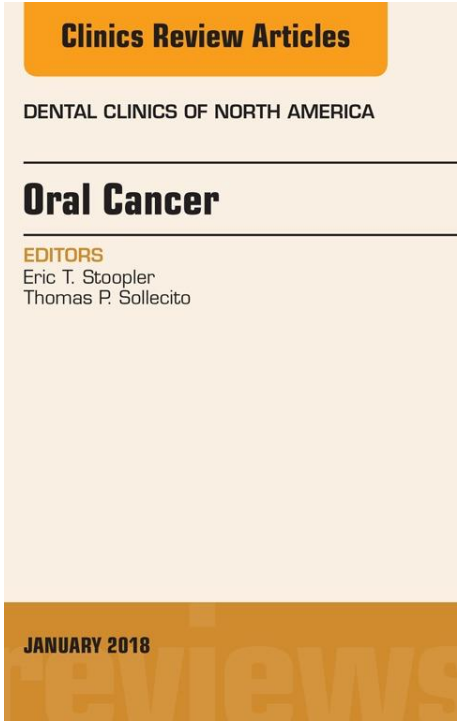
Thomas P. Sollecito, DMD, FDS RCSEd
Professor and Chair of Oral Medicine
University of Pennsylvania
School of Dental Medicine

Perelman School of Medicine
Abramson Cancer Center

# General Disclosure

Thomas P. Sollecito, DMD

- Serve on the following Scientific or Editorial Boards
  - Former ADA Council of Scientific Affairs
  - AAOM Board of Trustees
- Neither I nor members of my immediate family have any known financial relationships with commercial entities that may be relevant to this presentation
  - Except: Honorarium



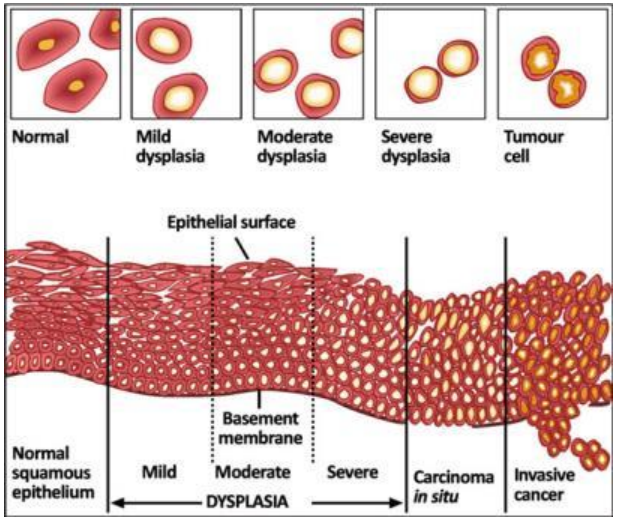
LOVE

# OPMD

- Oral Leukoplakia
  - Homogeneous
  - Nonhomogeneous
- Oral Erythroplakia
- Proliferative Verrucal Leukoplakia
- OSMF
- Palatal lesions in reverse smoking
- Actinic keratosis
- OLP
- Discoid lupus erythematous
- Dyskeratosis congenita

# Dysplasia

- **Mild:** alterations are limited to the basal and parabasal layer (lower 1/3rd)
- **Moderate:** alterations from the basal layer to the midportion of the spinous layer (midpoint)
- **Severe:** alterations from the basal layer to the level above the midpoint of the epithelium (upper 1/3rd)



# Dysplasia

## Cancers from dysplastic lesions develop

**Pathology Report**

Penn Oral Pathology Services

University of Pennsylvania Health System
3600 Spruce Street - 2 Maloney
Philadelphia, PA 19104
(215) 662-2597 Fax: (215) 614-0640
Dr. Alawi Direct: (215) 573-7638

[redacted]

| Accession #: | 1513706 |
|---|---|
| Procedure Date: | 3/24/2015 |
| Received Date: | 3/25/2015 |
| Report Date: | 3/26/2015 |
| Report Time: | 4:32 PM |

[redacted]

**DIAGNOSIS**

Tongue, left lateral border: **EPITHELIAL DYSPLASIA, MILD, SEE NOTE**

**Pathology Report**

Penn Cutaneous Pathology Services

University of Pennsylvania Health System
3600 Spruce Street - 2 Maloney
Philadelphia, PA 19104
(215) 662-2597 Fax: (215) 614-0640

[redacted]

| Accession #: | 1640560 |
|---|---|
| Procedure Date: | 8/17/2016 |
| Received Date: | 8/18/2016 |
| Report Date: | 8/19/2016 |
| Report Time: | 3:47 PM |

[redacted]

**DIAGNOSIS**

Tongue, left: **SQUAMOUS CELL CARCINOMA IN-SITU**

**Microscopic Description:**
**Tongue, left** - Atypical keratinocytes involve all layers of the epidermis. Associated parakeratotic scale is present.

# Dysplasia Considerations: To Treat or Not to Treat

- Dysplasia in Leukoplakia, Erythroplakia and PVL = have an equal MTR

- Treatment prevents Malignant Transformation
- Treatment does no harm

# Dysplasia

- Affects 2.5 to 5 per 1000 of population
- Reports of progression to cancer vary greatly from 6% to 36% at an annual rate of 1.36% (95% CI, 0.69%–2.03%)
- High risk of recurrence even after surgical excision (up to 35%)

van der Waal et al Oral Onc 1997
Reibel et al Crit Rev Oral Biol 2003
Mehannaet al Head and Neck 2009
Scully C. Med Oral Patol Oral Cir Bucal 2011

# Dysplasia

- **Poor inter and intra-observer agreement**
  - Range of 35.8 – 92.8%
  - 72 pathologists at a scientific meeting
  - Range of diagnosis agreement from 1-78%
- **Difficult to assess risk of transformation due to subjectivity of system**

Pindborg, Reibel and Holmstrup. Oral Pathol 1985
Abbey LM, Kaugars GE, Gunsolley JC, et al. OOOE 1995
Geetha KM, Leeky M, Narayan TV, et al. J Oral Maxillofac Pathol 2015;19

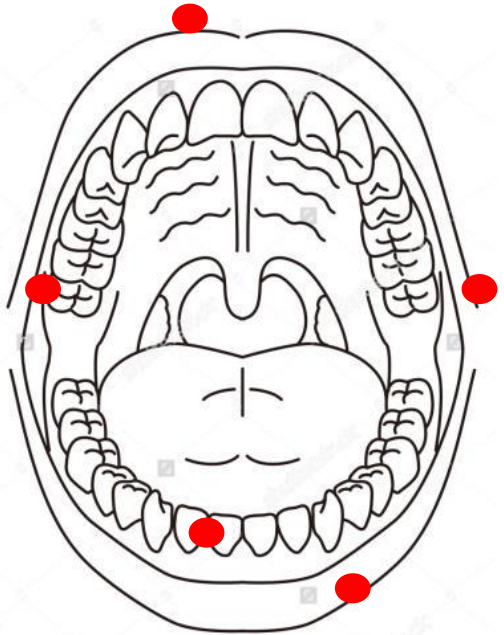
# Leukoplakia to Dysplasia

- Frequency of epithelial dysplasia in leukoplakia is approximately 1% to 30%.
- Non-homogenous OLs much higher chance of being dysplastic (12.63-fold) or demonstrating a focus of carcinoma (8.9-fold) compared with homogeneous OL.
- Estimated overall MTR is 3.5% and typically occurs within the first 5 years.
- A cross-sectional study in the US reported the OL sites with the highest prevalence of severe dysplasia or carcinoma insitu were the floor of mouth (13.5%) and tongue (5%).

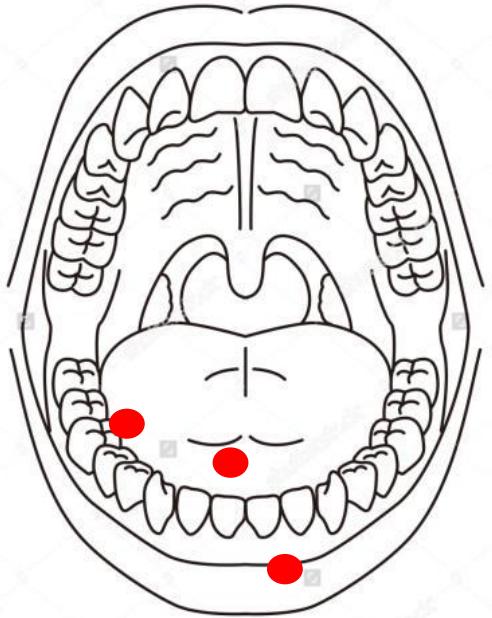
Pindborg JJ et al J Oral Pathol 1972; Gopinath D et J Clin Diagn Res 2016
Warnakulasuriya S et al J Oral Pathol Med 2016; Reibel J. Crit Rev Oral Biol Med 2003

# Leukoplakia

**70% of Leukoplakia: Lip Vermilion, Buccal Mucosa, Gingiva**

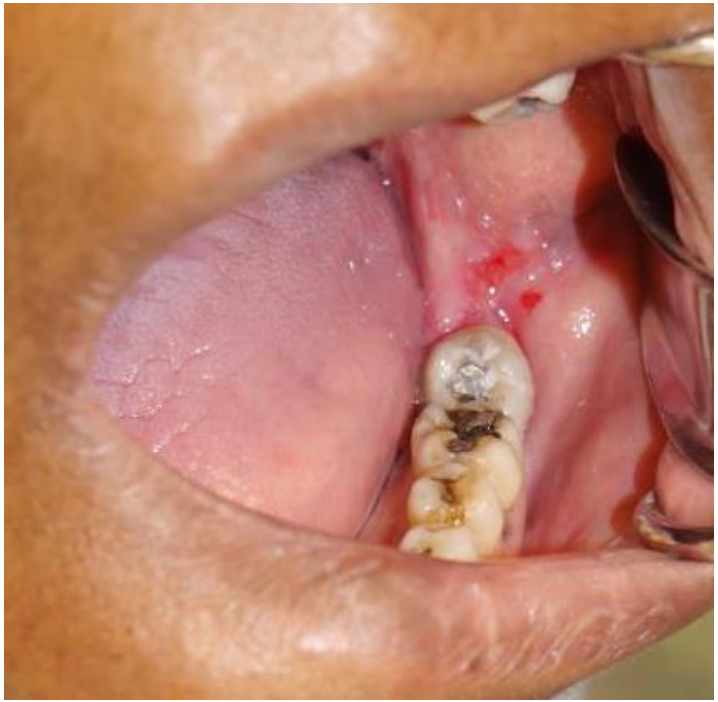


**90% of Dysplasia: Tongue, Lip Vermilion, and FOM**

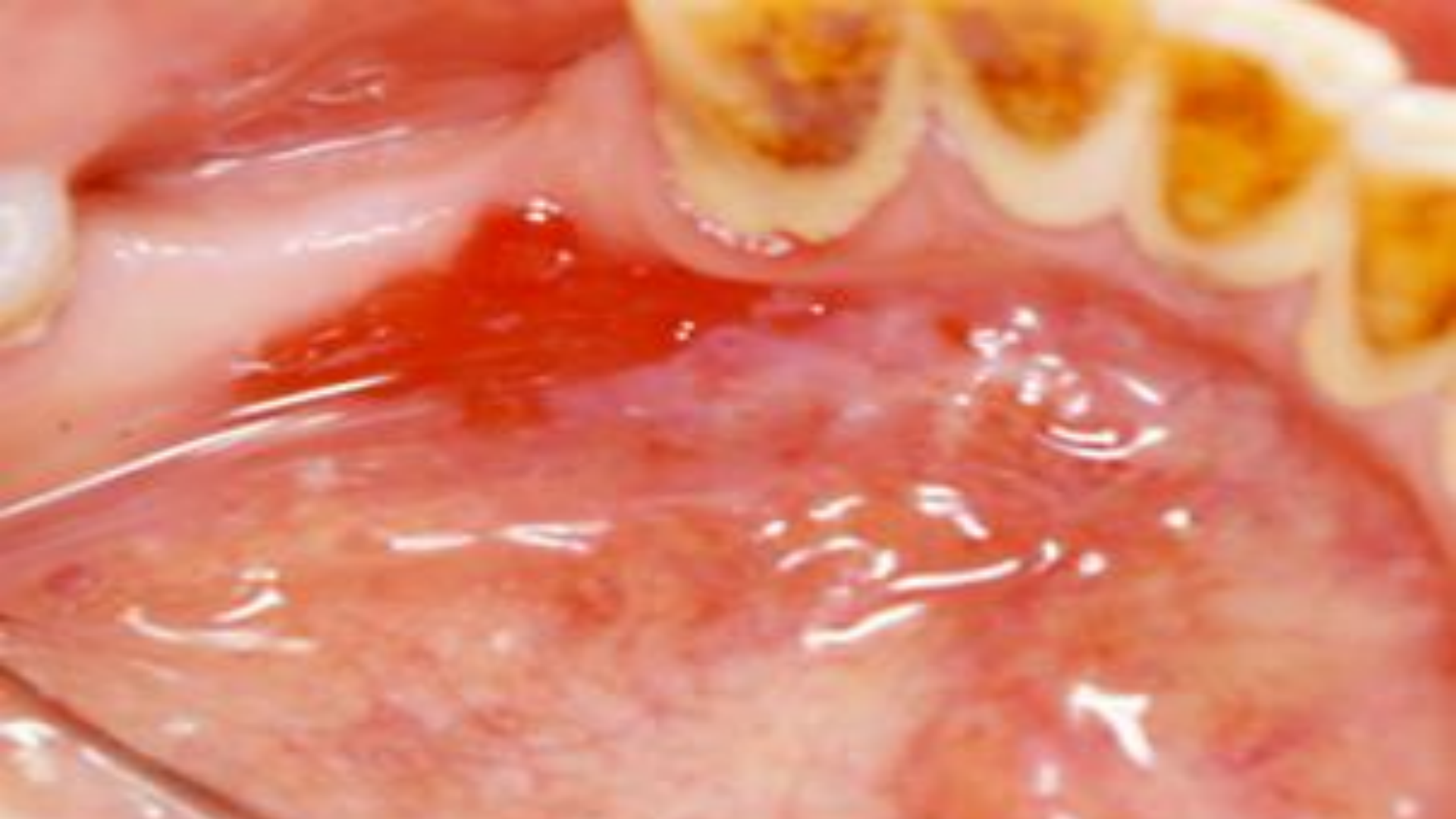


# Erythroplakia

- ***"Almost all true erythroplakias demonstrate significant epithelial dysplasia"*** *–Neville, Damm, Allen, and Bouquot* **(90%)**
- Cause of erythroplakia is unknown
- Predominantly a disease of older men
- Multiple lesions are often present
- Tongue, floor of mouth and soft palate are the most commonly involved subsites
- If not an OSCC, OE high potential for MT among OPMDs with an MTR, ranging from 14% to 50%.



Bouquot JE, Ephros H.. Pract Periodontics Aesthet Dent 1995



# Proliferative Verrucous Leukoplakia

- **Proliferative** (slow-growing) **Verrucous Leukoplakia** (warty, verrucal, exophytic, keratotic lesions develop within areas of leukoplakia)
- Single white lesion that with time becomes multifocal, growing slowly and progressively
- Predilection for elderly women (4:1), no racial predilection
- All sites in the oral cavity can be affected (no site predilection)—(1) gingiva (mandible > maxilla), (2) buccal mucosa
- High MTR (60%-100%)
- Frequent recurrences after total excision (87%–100%)
- High mortality rates (30%–50%)

oral pathology

Editor
JAMES J. SCIUBBA, D.M.D., Ph.D.
American Academy of Oral Pathology
Department of Dentistry
Long Island Jewish-Hillside Medical Center
New Hyde Park, New York 11042

Proliferative verrucous leukoplakia

A long-term study of thirty patients

Louis S. Hansen, D.D.S.,* James A. Olson, D.D.S.,** and Sol Silverman, Jr., D.D.S.,***
San Francisco, Calif.

DEPARTMENT OF STOMATOLOGY, UNIVERSITY OF CALIFORNIA SAN FRANCISCO

Up to 6% of oral leukoplakia, a relatively common mucosal disease, can be expected to become malignant. This report describes a long-term study of 30 patients in whom a particular form of leukoplakia was identified and labeled *proliferative verrucous leukoplakia* (PVL), a disease of unknown origin, which exhibits a strong tendency to develop areas of carcinoma. PVL begins as a simple hyperkeratosis but tends to spread and become multifocal. PVL is slow-growing, persistent, and irreversible, and in time areas become exophytic, wartlike, and apparently resistant to all forms of therapy as recurrence is the rule. The disease was most commonly seen in elderly women and had been present for many years. Patients were followed for 1 to 20 years. Thirteen died of or with their disease, 14 were alive with PVL, and 3 were alive without PVL at last contact. PVL rarely regressed despite therapy. All patients who died had persistent or recurrent disease. PVL appears to constitute a continuum of hyperkeratotic disease, ranging from a simple hyperkeratosis at one end to invasive squamous cell carcinoma at the other. Microscopic findings are dependent upon the stage of the disease's development and the location and adequacy of the biopsy.
(Oral Surg. Oral Med. Oral Pathol. 60:285-298, 1985)

In 1978 the WHO Collaborating Centre for Oral Precancerous Lesions proposed that leukoplakia be defined as a clinical white patch of the oral mucosa that cannot be characterized clinically or pathologically as any other disease.[1] Even though this excludes such diseases as lichen planus, discoid lupus erythematosus, white sponge nevus, candidiasis, and hyperkeratoses due to cheek- and lip-biting, oral leukoplakia must, by this definition, be regarded as a relatively common mucosal disease. Its prevalence around the world in random population groups 14 years of age and older has been reported to range from 0.2% to 24.8%, depending on clinical criteria used, geographic location of the population group, intraoral location, and cultural habits.[2-17] In most studies prevalence seems to center around 3% to 5%.

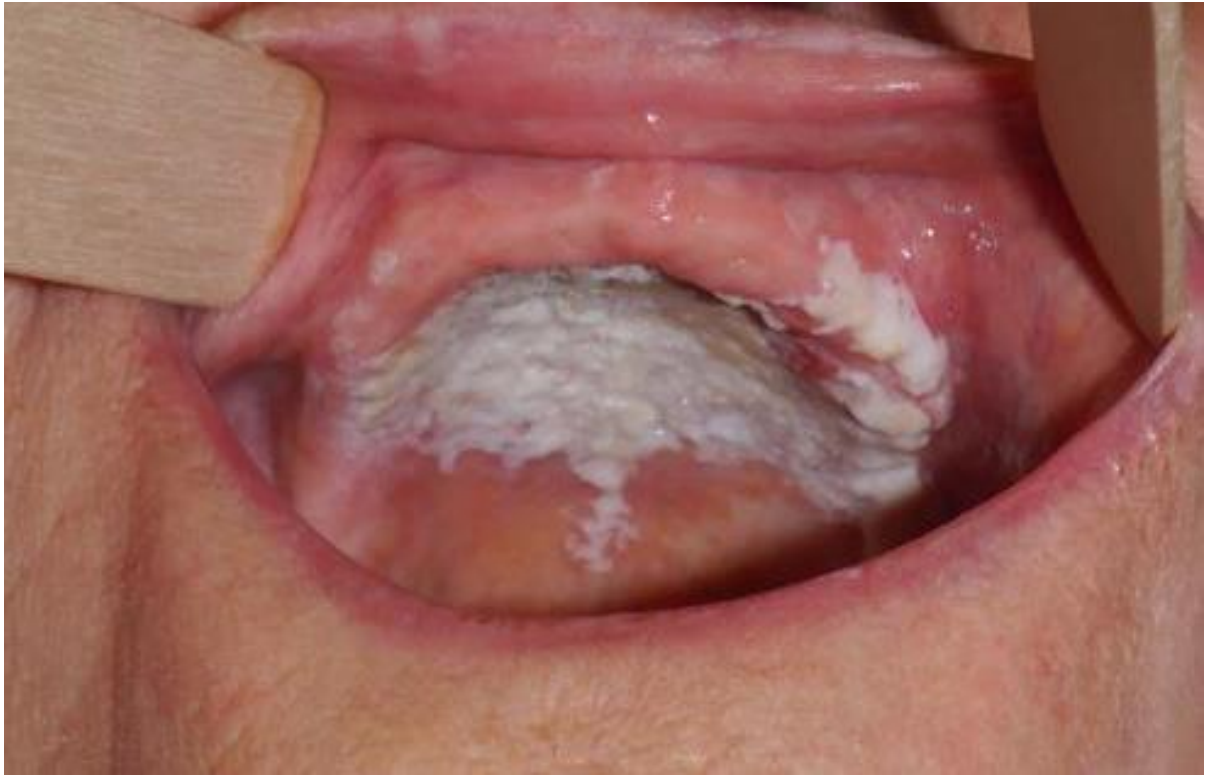
Many studies have been undertaken to assess the fate of these lesions.[4,7,16,17] Most were designed to establish the rate of malignant transformation. Bánóczy,[17] in a study of 670 patients followed for more than 30 years, reported that the lesions disappeared in 31.0% of her patients, improved in 29.7%, remained unchanged in 25.8%, spread in 7.5%, and became malignant in 6%. Others have found rates of malignant transformation ranging from 0.13% to 17.5% and averaging around 4.5% to 6.0%.[4] The variation in transformation rates appears to be related to such variables as period of observation, age, sex, location and type of leukoplakia, treatment methods, geographic location (probably reflecting differences in oral habits and local customs), and various etiologic factors.[4,12-14,16,17,19,20,27] In Bánóczy's study there was a very significant correlation ($p$ less than 0.001) between clinical type and malignant

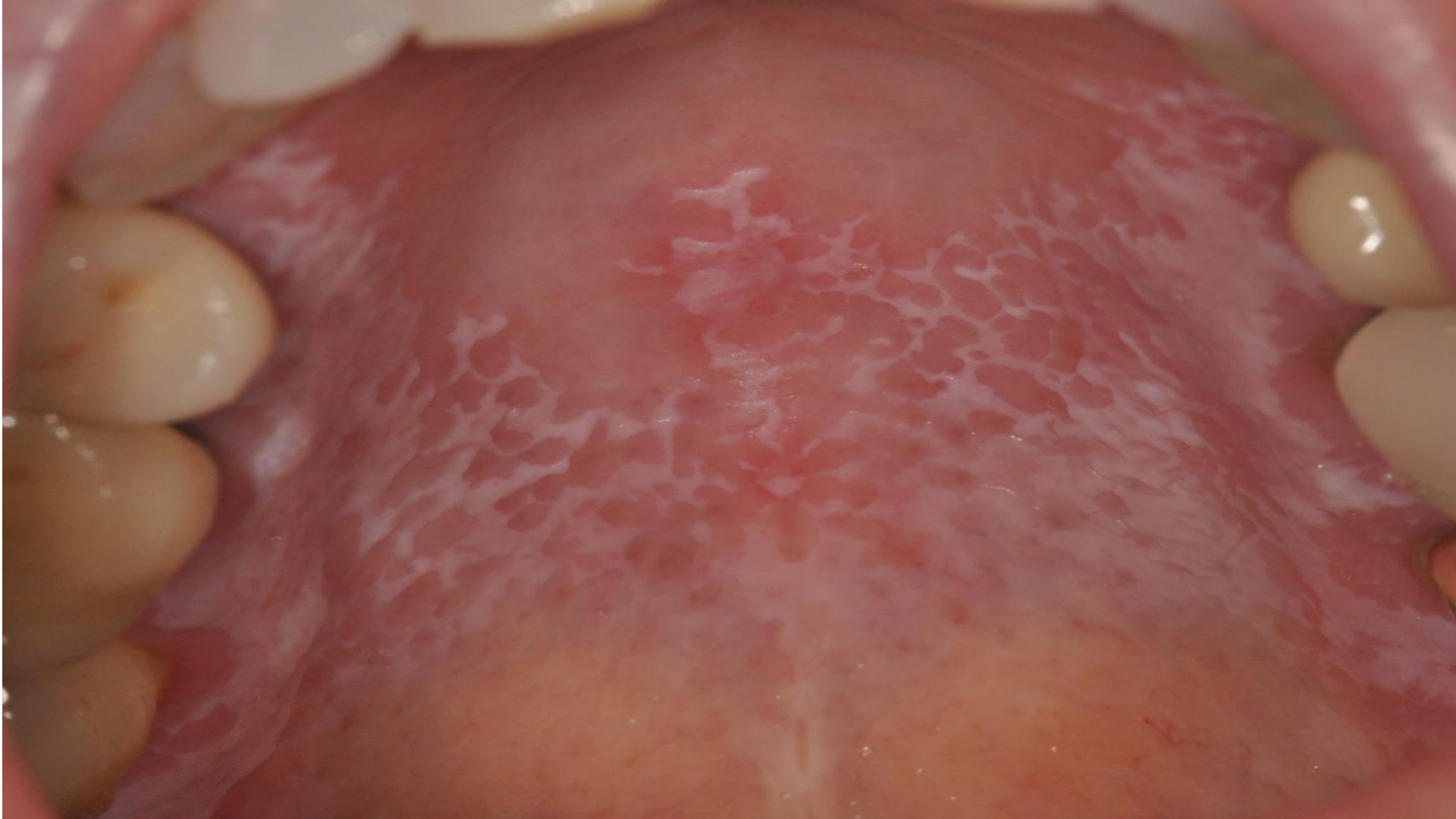
This study was supported in part by a grant from the Donald T. Elliott Oral Cancer Research Fund and National Cancer Institute Grant No. CA 17914-08
*Professor and Chairman, Division of Oral Pathology.
**Associate Clinical Professor, Division of Oral Medicine.
***Professor and Chairman, Division of Oral Medicine.

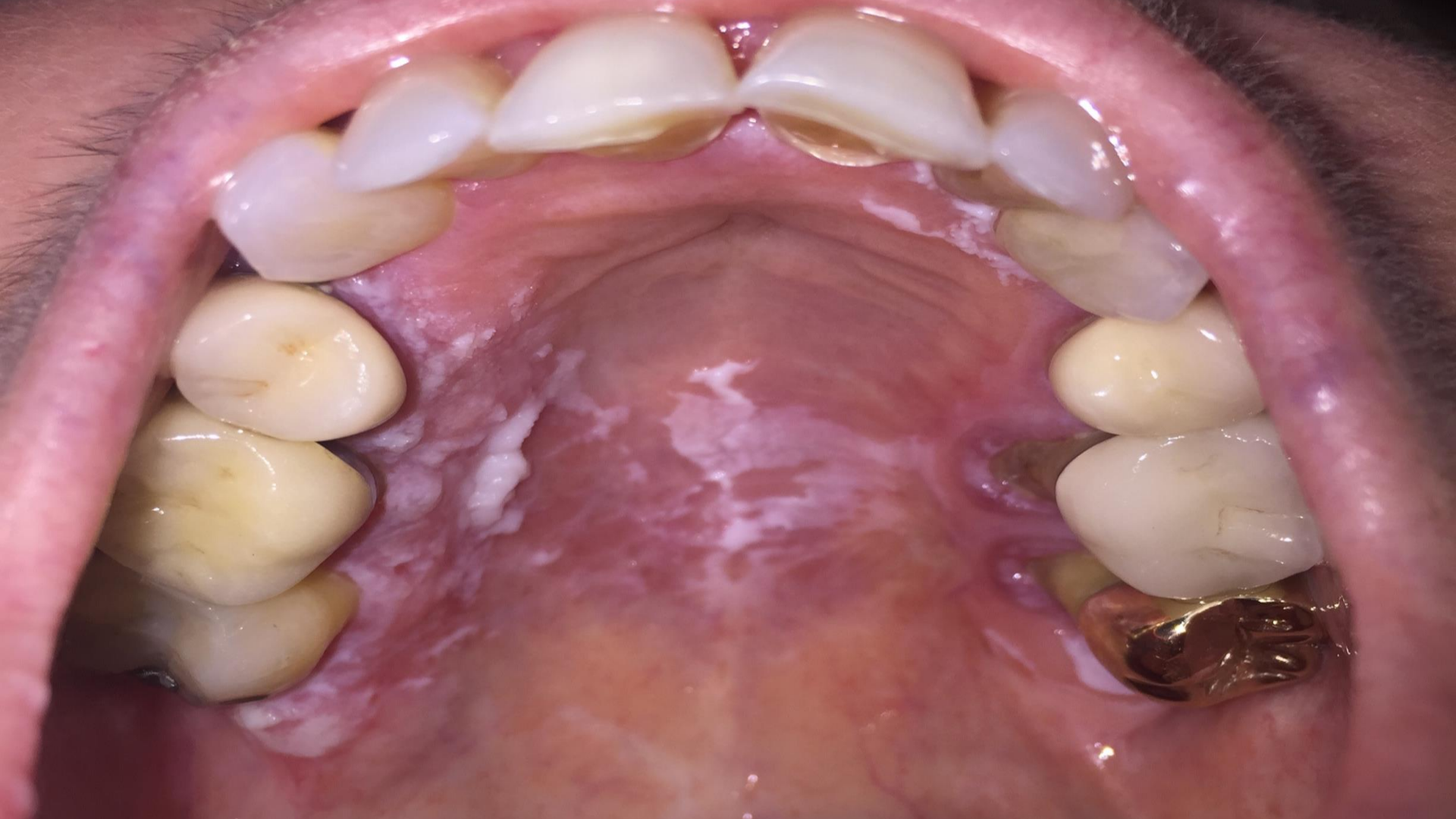
285


Bagan JV J Oral Pathol Med 2003
Silverman S Jr Cancer 1984
Bagan JV Oral Oncol 2011

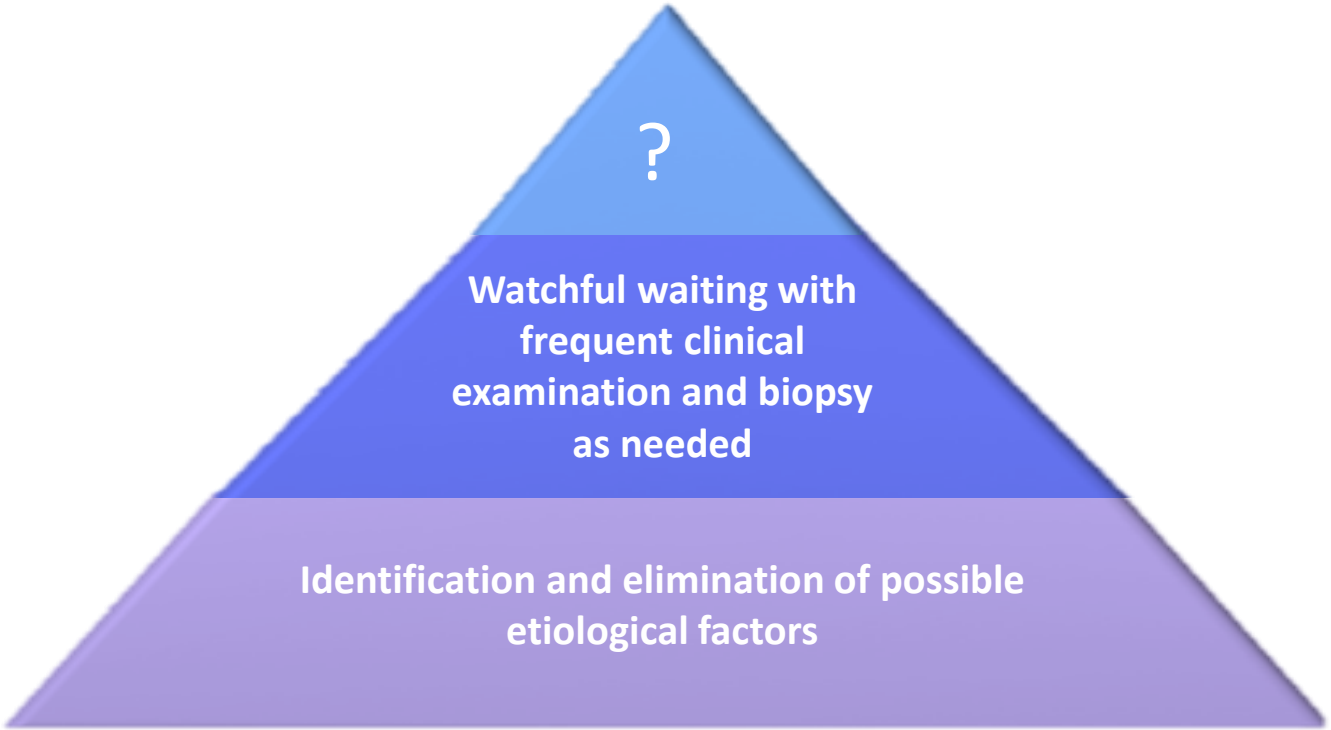
# Proliferative Verrucous Leukoplakia







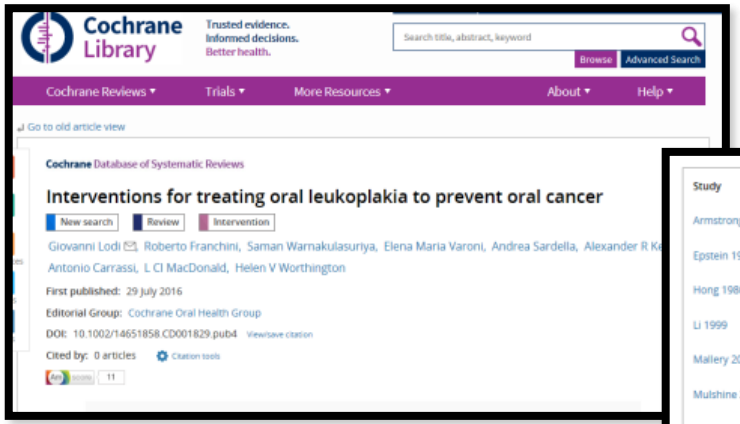
# Dysplasia Treatment



# ? Dysplasia Treatment

- Medical Interventions
  - Chemoprevention
- Surgical Interventions
  - Blade
  - Laser $CO_{2,}$
  - Cryosurgery
  - Photodynamic Therapy

# OPMD - Medical Treatment




| Study | Arms | Active treatment | Placebo |
|---|---|---|---|
| Armstrong 2013 | Bowman Birk inhibitor concentrate vs placebo | 24/67 | 19/65 |
| Epstein 1994 | Topical bleomycin vs placebo | 0/10 | 1/12 |
| Hong 1986 | Systemic 13-cis-retinoic acid (from 1 to 2 mg/kg per day) vs placebo | 2/24 | 2/20 |
| Li 1999 | Systemic and topical tea vs placebo | 3/32 | 2/32 |
| Mallery 2014 | Freeze-dried black raspberry gel vs placebo gel | 0/22 | 0/18 |
| Mulshine 2004 | Ketorolac oral rinse vs placebo | 1/38 | 0/19 |
| Nagao 2015 | Beta carotene and vitamin C vs placebo | 5/23 | 5/23 |
| Papadimitrakopoulou 2008 | Celecoxib vs placebo | 3/32 | 1/18 |
| Piattelli 1999 | Topical 13-cis-retinoic acid vs placebo | 0/5 | 1/5 |
| Sankaranarayan 1997 | Vitamin A (300,000 IU per week) vs placebo | 8/50 | 12/55 |
| Sankaranarayan 1997 | Beta carotene (360 mg per week) vs placebo | 9/55 | 12/55 |
| Singh 2004 | Lycopene (8 mg or 4 mg) vs placebo | 0/40 | 0/18 |
| Stich 1988 | Vitamin A (200,000 IU per week) vs placebo | 9/30 | 2/35 |
| Sun 2009 | Chinese herbal mixture vs placebo | 1/60 | 7/60 |

vs = versus

Lodi G et al. Interventions for treating oral leukoplakia to prevent oral cancer. Cochrane Database Syst Rev 2016

# OPMD Medical Treatments

- None of the studies provided evidence that active treatment reduced the risk of oral cancer > placebo
- In 2 RCT's, MT occurred more frequently in an active treatment group after discontinuing the products (small sample size)

Nadeau C, Kerr AR, Dent Clin N Am 62 (2018) 1–27

Medical interventions with randomized placebo-controlled studies

| Agent | Rationale | Formulations | Trial (Endpoint) |
|---|---|---|---|
| Retinoids | Inhibiting growth and inducing cell differentiation | Systemic: 13-cis-retinoic acid[86] | +(HR) |
| | | Topical: 0.1% 13-cis-retinoic acid gel 3×/d × 4 mo[115] | – |
| Vitamin A | Inhibiting growth and inducing cell differentiation | Vitamin A 200,000 IU po/wk × 6 mo[83] | +(CR), +(HR) |
| | | Vitamin A 300,000 IU po/wk × 12 mo[81] | +(CR) |
| Carotenoids | Antioxidants/ scavenge free reactive oxygen species | β-carotene 10 mg/vitamin C 500 mg po daily × 12 mo[82] | – |
| | | β-carotene 360 mg/wk po × 12 mo[81] | +(CR) |
| | | Lycopene 4–8 mg/d po × 3 mo[84] | +(CR), +(HR) |
| Green tea extracts | Antioxidants due to tea polyphenols (ie EGCG) | Green tea capsules 3g 4×/d plus extract applied to lesions 3×/d × 6 mo[87] | – |
| | | Green tea extracts 500, 750, 100 mg/m$^2$ po tid × 3 mo[116] | |
| Black raspberry | Antioxidants due to high anthocyanin content | Topical: black raspberry bioadhesive gel daily × 3 mo[88] | – |
| Chinese herbs | Anti-inflammatory | Zengshengping 4 tablets po tid × 8–12 mo[117] | – |
| Bowman-Birk inhibitor | Protease inhibitor vs carcinogenesis-associated proteolysis | Topical: Bowman-Birk inhibitor concentrate mouthwash swished bid × 6 mo[118] | – |
| Nonsteroidal anti-inflammatory drugs | Cyclooxygenase inhibition | Topical: 0.1% ketorolac rinse once/d × 3 mo[119] | – |
| | | Celecoxib 100, 200, or 400 mg po bid × 3 mo[120] | |
| Bleomycin | Chemotherapy | Bleomycin in DMSO (1%) application once daily × 14 d[85] | – |
| Erlotinib | Epidermal growth factor receptor inhibition | Erlotinib 150 mg/d po × 12 mo[89] | – |

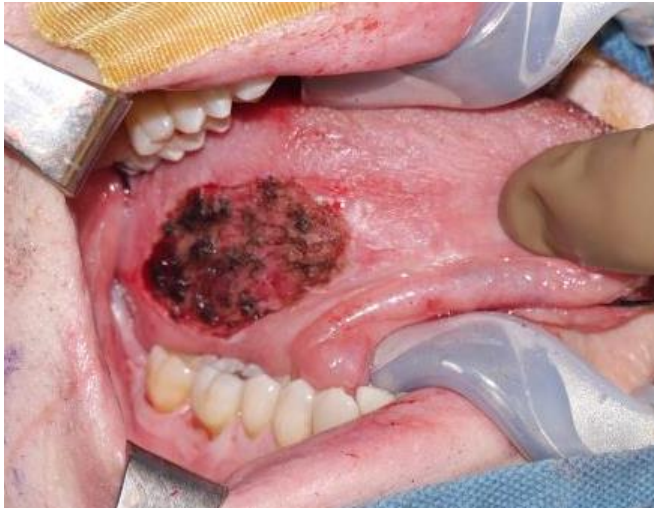
*Abbreviations:* +, positive trial; –, negative trial; CR, complete remission; DSMO, dimethyl sulfoxide; EGCG, epigallocatechin gallate; HR, histologic remission.

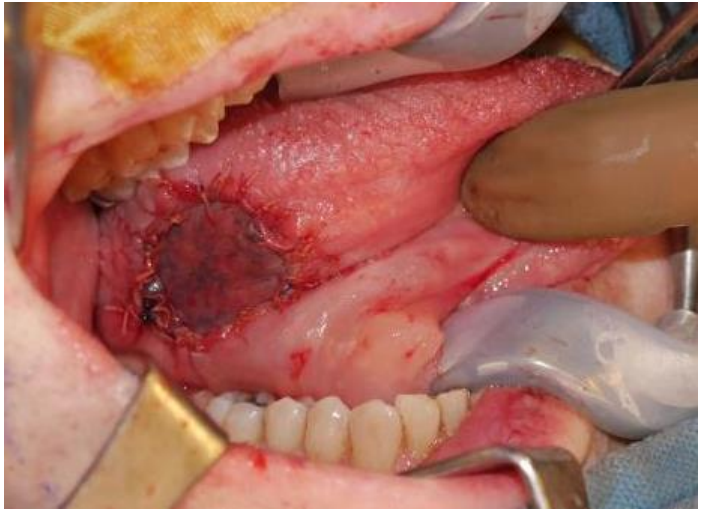
# OMPD— Surgical Treatment

- No randomized clinical trial exists for surgery or laser evaporation/ablation

- Studies are heterogeneous
- Small sample size
- Blend of OPMDs
- Population lacks a representative spectrum of histology
- Follow-up (most <5 years).

# Dysplasia—Management



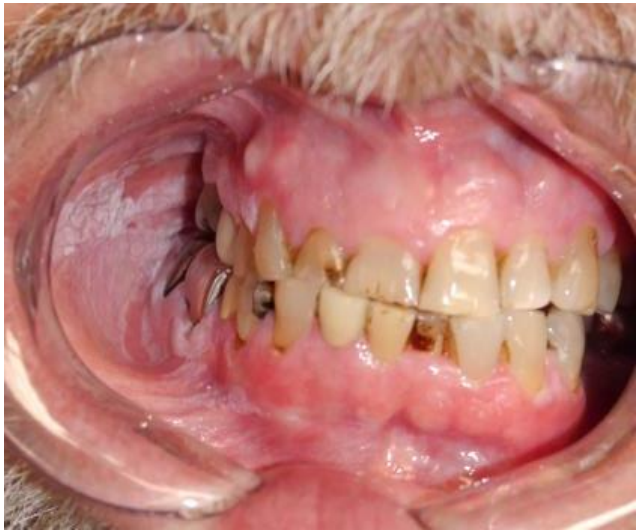


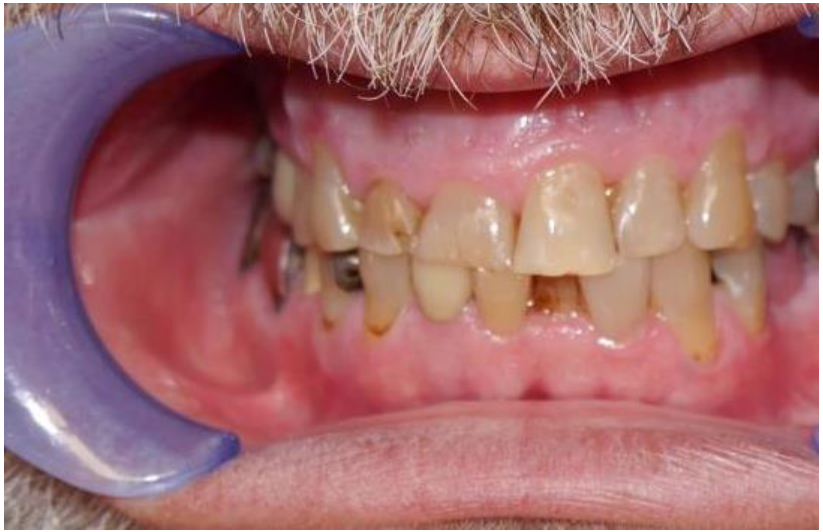
# Traditional Excisional Surgery

- A large systematic review demonstrated a significantly reduced MT rate in patients with dysplastic OPMDs (5.4% vs 14.6%)
  - Many of the studies included in the review were poor-quality and showed significant heterogeneity
- Large retrospective study over a 16-year period in 207 patients with graded dysplastic OPMDs reported no statistical difference in MTRs

Mehanna HM et al. Head Neck 2009
Arduino PG, et al. J OralPathol Med 2009

# Laser Surgery





# Laser Treatments

- Review of $CO_2$ laser use on OPMDs included 17 studies reporting recurrence rates of 3% to 41% and MTRs of 0% to 15% with a 1 – 5 year follow-up
- In a cohort of 590 patients lesion appearance, grade of dysplasia, and the presence of a lichenoid infiltrate were predictive for disease-free survival (ie, no evidence of recurrence)

Mogedas-Vegara A et al J Craniomaxillofac Surg 2016
Thomson PJ, Int J Oral Maxillofac Surg 2017;46

# Cryotherapy and PDT

- Cryo weak studys with limited follow up
- Prospective topical PDT study on a cohort of 147 dysplastic OPMDs
  - mean follow-up > 7 years
  - complete response rate was 81% and correlated with grade of dysplasia.
  - recurrence rate was 11.6%, and an MT was noted in 7.5% of the patients.

Yu CH et al.J Formos Med Assoc 2014
Jerjes W et al. Lasers Surg Med 2011

# Do No Harm

- Potential cancer promotional stimulus because proliferation of remaining dormant cancer stigmatized clones of cells in the border zone area of the removed leukoplakia may result in frank carcinoma to occur (Holmstrup, 2009).

Holmstrup P, Dabelsteen E. Oral leukoplakia-to treat or not to treat. Oral Dis 2016;22(6):494–7.

# OPMD—Risk of MT

**Box 2**
**Risk factors for oral potentially malignant disorders malignant transformation**

Female gender

Age greater than 45 years old

Leukoplakia in nonsmoker

Nonhomogeneous type

Size greater than 200 $mm^2$

Higher grade of dysplasia

High risk site (floor of mouth, ventrolateral tongue, retromolar area, soft palate)

Nadeau C, Kerr AR, Dent Clin N Am 62 (2018) 1–27

# Dysplasia—Management

- OPMDs with high-grade dysplasia are more than twice as likely to undergo MT (mild/moderate 10.3% vs severe 24.1%)

Holmstrup P, Vedtofte P, Reibel J, et al. Long-term treatment outcome of oral premalignant lesions. Oral Oncol 2006;42(5):461–74.
Mehanna HM, Rattay T, Smith J, et al. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head Neck 2009;

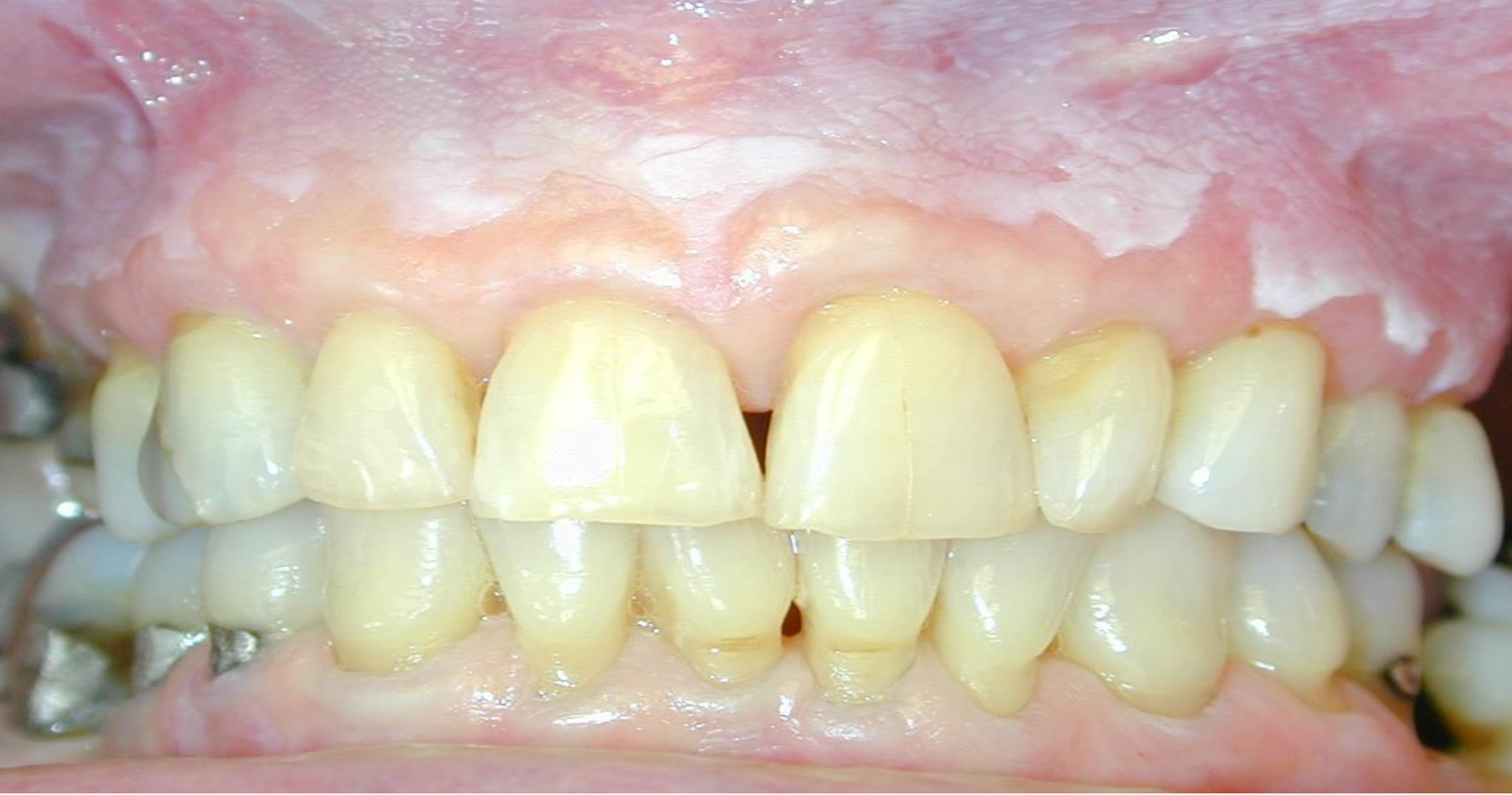


Photo courtesy Dr P. Michele Williams

J Oral Path Med 1996; 25: 49-54.

# Dysplasia: ? Treat

- Progression of dysplasia
- Texture
- Color
- Location involved
- Size
- ***Clinical Instinct***

- Future:
- Ability to differentiate molecularly high risk lesion from lower risk
- Management based on improved predictive value