Oral Cancer in 2013: The Good, the Bad and the Ugly

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Outline
- Risk factors
  - Screening technologies
  - Diagnostic techniques
  - Therapeutic modalities
  - Management of treatment complications
Risk Factors

- Intrinsic
  - Nutrition
  - Anemia
  - Immunosuppression
  - Oncogenes

- Extrinsic
  - Tobacco
  - Alcohol
  - Tobacco AND alcohol (40x risk)
  - Ultraviolet radiation
  - Microbes
The real reason dinosaurs became extinct
Tobacco Advertising

- Increased graphic warnings for cigarettes scheduled for September 2012
- Congress told the images would be frightening and disturbing to smokers
- Died a "political death"
"STANDARD" SERVINGS OF ALCOHOLIC BEVERAGES

A standard serving of an alcoholic beverage is 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof spirits. These serve as a reference point as all other alcoholic beverages are measured against these amounts. For example, a 2.5 ounce serving of 80-proof spirits is considered a standard serving. However, it is important to note that the amount of alcohol in a serving can vary depending on the type of beverage and the brand. It is always best to drink responsibly and to be aware of the number of servings you consume.
Unhealthy Alcohol Use

### Category of Use

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Definition and Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risky use</td>
<td>&lt;65 years: &gt;7 drinks/week or &gt;3 drinks/occasion  &lt;65 years: &gt;14 drinks/week or &gt;4 drinks/occasion</td>
</tr>
<tr>
<td>Problem drinking</td>
<td>Varies Alcohol-related consequences, e.g., &quot;hangover&quot;</td>
</tr>
<tr>
<td>Alcohol abuse, harmful use</td>
<td>5% Failure to fulfill major role obligations; use in hazardous situations; alcohol-related legal problems; social or interpersonal problems</td>
</tr>
<tr>
<td>Alcohol dependence, alcoholism</td>
<td>4% Clinically significant impairment or distress, plus 3 or more of the following: tolerance, withdrawal, excessive time spent obtaining, using or recovering from use, drinking more or longer than intended, inability to control use, continued use despite problems</td>
</tr>
</tbody>
</table>

Saitz R. NEJM 2005;352:596-607
Ultraviolet Radiation

“The first six are for bullets. This one here’s for lip balm.”

[Image of various lip balm products]
Human Papillomavirus

- Over 40 types infect skin and mucosa
- Infections normally cleared over time
- Persistent infections associated with
  - Genital warts
  - Laryngeal warts (respiratory papillomatosis)
  - Cancer of the cervix, vulva, vagina, penis, anus, oropharynx, esophagus (?), conjunctiva (?), paranasal sinuses (?), bronchi (?)

<table>
<thead>
<tr>
<th>Disease</th>
<th>HPV type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common warts</td>
<td>2, 7</td>
</tr>
<tr>
<td>Plantar warts</td>
<td>1, 2, 4, 63</td>
</tr>
<tr>
<td>Flat warts</td>
<td>3, 10, 8</td>
</tr>
<tr>
<td>Anogenital warts</td>
<td>6, 11, 4, 44 and others</td>
</tr>
<tr>
<td>Anal lesions</td>
<td>6, 16, 18, 31, 53, 58</td>
</tr>
<tr>
<td>Genital cancers</td>
<td></td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>more than 15 types</td>
</tr>
<tr>
<td>Focal epithelial hyperplasia (oral)</td>
<td>13, 32</td>
</tr>
<tr>
<td>Oral papillomas</td>
<td>6, 7, 11, 16, 32</td>
</tr>
<tr>
<td>Oropharyngeal cancer</td>
<td>16</td>
</tr>
<tr>
<td>Verucous cyst</td>
<td>60</td>
</tr>
<tr>
<td>Laryngeal papillomatosis</td>
<td>6, 11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer area</th>
<th>Average Annual Number of cases</th>
<th>HPV Attributable (Estimated)</th>
<th>HPV 16/18 Attributable (Estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11,967</td>
<td>11,500</td>
<td>9,100</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,136</td>
<td>1,600</td>
<td>1,400</td>
</tr>
<tr>
<td>Vagina</td>
<td>729</td>
<td>500</td>
<td>400</td>
</tr>
<tr>
<td>Penis</td>
<td>1,046</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>Anus (woman)</td>
<td>3,089</td>
<td>2,900</td>
<td>2,700</td>
</tr>
<tr>
<td>Anus (men)</td>
<td>1,678</td>
<td>1,600</td>
<td>1,500</td>
</tr>
<tr>
<td>Oropharynx (woman)</td>
<td>2,370</td>
<td>1,500</td>
<td>1,400</td>
</tr>
<tr>
<td>Oropharynx (men)</td>
<td>9,356</td>
<td>5,900</td>
<td>5,600</td>
</tr>
<tr>
<td>Total (women)</td>
<td>21,291</td>
<td>18,000</td>
<td>15,000</td>
</tr>
<tr>
<td>Total (men)</td>
<td>12,080</td>
<td>7,900</td>
<td>7,600</td>
</tr>
</tbody>
</table>
HPV and Oral Cancer

- PubMed (6/14/13)
  - Human papillomavirus
    30,614 published manuscripts
  - Human papillomavirus + oral
    2,189 published manuscripts
  - Gillison + human papillomavirus
    61 published manuscripts
  - Gillison + human papillomavirus + oral
    33 published manuscripts

What does the data show?

- HPV is an independent risk factor for oral and oropharyngeal squamous carcinoma
- Multiple studies; multiple institutions
- ~30% prevalence rate of HPV detection in H&N cancer surgical specimens
- Higher prevalence in oropharyngeal lesions (~35%) than laryngeal (~25%) or oral (<25%) lesions
Which HPV is responsible?

- HPV-16
  - 86.7% of oropharyngeal lesions
  - 68.2% of oral lesions
  - 69.2% of laryngeal lesions

Is HPV-related H&N SCC different?

- Yes
- Better prognosis
- Better clinical outcome

How big is the problem?

Prevalence of Oral HPV Infection in the United States, 2009-2010

6.9% -- higher in men
Sex & Oropharyngeal Cancer

- Sexual behavior is associated with oropharyngeal carcinoma
- Related to lifetime # of sex partners
- Vaginal sex and oral sex
- Open-mouth kissing
- HPV exposure precedes oropharyngeal cancer by at least 10 years

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The Prevalence and Incidence of Oral Human Papillomavirus Infection Among Young Men and Women, Aged 18–30 Years

Robert K. L. Pickard, MS, MPH, EdM,* Wei Hong Xiao, MD,* Tatyana R. Brovman, MS,* Xin He, PhD,† and Mauss I. Gillison, MD, PhD*†

Sex Trans Dis 2012;39:559-66

Oral Sexual Behaviors Associated with Prevalent Oral Human Papillomavirus Infection

Eleanor R. honest,††* and Mauss I. Gillison††*

Department of Medicine, Johns Hopkins Bloomberg School of Public Health, Department of Oncology, and the Oncology Branch, National Cancer Institute, Bethesda, Maryland.

Increased risk with oral sex and open-mouth kissing

J Infect Dis 2009;199:1263-69

Michael Douglas: Oral sex gave me cancer

Actor Michael Douglas said he was first diagnosed with throat cancer at age 55, and the disease is believed to be connected to HPV, putting him among the growing number of people falling victim to the virus.
Unanswered Questions

- Does HPV-associated H&N cancer develop differently than analogous cervical cancer?
- Are tobacco and alcohol use co-factors in HPV-associated H&N cancer?
- Do we need to screen for oropharyngeal HPV infection in high-risk groups, e.g., smokers and drinkers?
Unanswered Questions

- Do we treat HPV-positive premalignant, i.e., dysplastic, oropharyngeal lesions differently?
- Do we treat HPV-positive malignant oropharyngeal lesions differently?
- Would some oropharyngeal cancers be prevented by HPV vaccination?

HPV Prophylactic Vaccines and the Potential Prevention of Noncervical Cancers in Both Men and Women

Mona L. Elleen, M.D.1
Anil K. Chaturvedi, M.D.2
Douglas K. Lowy, M.D.3

1Division of Head and Neck Surgery, Johns Hopkins Hospital, Baltimore, Maryland
2Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland
3Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland

Human papillomavirus (HPV) is a common cause of cervical cancer. In addition to its role in the development of cervical cancer and a number of genital and oropharyngeal malignancies, HPV-related malignancies include squamous cell carcinomas of the skin and esophagus, adenocarcinomas of the anus and vulva, and a subset of head and neck cancers. The efficacy of HPV vaccination in preventing infection at sites other than the cervix, vagina, and vulva is not known. Given that a substantial proportion of cervical cancer (approximately 70%) and even greater proportion of HPV-associated noncervical cancers (approximately 80%) to 90%) are caused by HPV16 and 18 (HPV types that are targeted by the currently available vaccines), current HPV vaccines may hold great promise (provided equivalent efficacy or all relevant anatomic sites is reduced in the burden of HPV-associated noncervical cancers. In addition to cervical cancer, Cancer 2006;113:199

HPV Vaccines – 3 Injections

Cervarix
Bivalent
Females 9-25
Cervical cancer (HPV 16, 18)

Gardasil
Quadrivalent
Females and males 9-26
Cervical cancer (HPV 16, 18)
Genital warts (HPV 6, 11)
Screening Technologies

- Vital dye (toluidine blue)
- ViziLite® / ViziLite® Plus with TBlue
- VELscope
- Identafi
- Exfoliative cytology
- Brush biopsy

Critical evaluation of diagnostic aids for the detection of oral cancer

Mark W. Lingen, John R. Kalmar, Theodore Karrson, Paul M. Speight
Variations on a Theme

- Microlux™
- OraScoptic™
Surgical Margins

Surgical Specimen

Identafi
**Violet Light** – Enhances Normal Fluorescence

**Amber Light** – Enhances Vasculature

**Diagnosis – Carcinoma *in situ***
Oral Cancer Detection

- 80% survival with localized disease
- 20% survival with distant metastasis

**EARLY DETECTION = BETTER SURVIVAL**

- 50% with metastasis at diagnosis
- 65% with clinical symptoms at diagnosis

Visual Clinical Examination

- High sensitivity
  - detect abnormality with ease

- Low specificity
  - diagnose abnormality with difficulty

Problem

- 15% of patients have mucosal abnormality (Bouquot, 1986)
- 25% of malignant lesions appear benign (Sandler, 1962, 1966)
- 30% of soft tissue lesions are misdiagnosed (Dimitroulis, 1992)
Problem

- Unsure which lesions require testing
- Uncomfortable performing scalpel biopsy
- Patients resist incisional biopsy
- NOT ALL LEUKOPLAKIAS BIOPSIED

Sandler (JADA, 1966)

- 118,000 VA patients
- 2,758 with visible mouth lesions
- 592 had cytology and biopsy
- 70 of 287 SCC THOUGHT BENIGN
- 20 of 28 CIS THOUGHT BENIGN
- 11 of 1,801 (-) cytologies BECAME MALIGNANT
Traditional Cytology

- 300,000 - 500,000 cells per smear
- Less than 0.005% abnormal cells
- Searching for a “needle in a haystack”
- People are not good searchers (proof reading)
Traditional Cytology
- Psychological habituation
  - eye sees abnormality
  - brain imposes expected pattern
- Sensitivity below threshold
  - don't detect abnormal cells

Did you see the typographical error in the last slide?
Folsom (Oral Surgery, 1972)

- 158,996 patients screened over 3 years
- 6,897 (4%) had oral lesions
- 148 cancers (2%) among oral lesions
- 41/148 (31%) **FALSE NEGATIVE CYTOLOGY**
Oral CDx™ (Brush Biopsy)
- Effective
- Easy to use
- Bridges the gap between visual exam and incisional biopsy
- Helps to determine which lesions merit an incisional biopsy
- ADA Seal of Acceptance

Oral CDx™
- Optimal sample – full transepithelial sampling
- Optimal search – adaptive, non-algorithmic computing
- Optimal interpretation – oral cytology specialists

EXFOLIATIVE CYTOLOGY
Only Surface Cells Captured
Broom sweep limited to superficial cells
4.5% Dysplasia or Malignancy in Clinically Benign Lesions

<table>
<thead>
<tr>
<th>BRUSH BIOPSY RESULT</th>
<th>SCALPEL BIOPSY RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malignant or Dysplastic</td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
</tr>
<tr>
<td>Atypical</td>
<td>15</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Not Done</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
</tr>
</tbody>
</table>

Screening for Oral Cancer: U.S. Preventive Services Task Force Recommendation Statement

DRAFT

Summary of Recommendation and Evidence
The U.S. Preventive Services Task Force (USPSTF) concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.
Clinical Features

- 90% of cases
  - lower lip
  - ventral tongue
  - floor of mouth

- Most cases present for at least 1 year as an asymptomatic lesion
Clinical Features

- Leukoplakic (white)
- Endophytic (ulcerating)
- Exophytic (fungating)
- Erythroplakic (red)
Diagnostic Techniques

- Scalpel biopsy
- Punch biopsy
**Multidisciplinary Therapy**

- Surgery
- Radiation therapy
- Combination therapy
- Periodic reassessment

**Prognosis**

- Depends on location and progression
  - More anterior location
  - No regional lymph node involvement
  - No distant metastasis

**Grading**

- Assessment of biologic behavior based on microscopic features of pleomorphism, cellular maturation, keratin production, etc.
- Grade I – well differentiated
- Grade II – moderately well differentiated
- Grade III – moderately differentiated
- Grade IV – poorly differentiated
Staging
- Assessment of survival based on a combination of factors
  - tumor size (T)
  - regional lymph node involvement (N)
  - distant metastasis (M)
- TNM system

TNM Staging
- TX – not assessed
- T0 – no evidence of tumor
- Tis – carcinoma *in situ*
- T1 – <2 cm
- T2 – 2-4 cm
- T3 – >4 cm
- T4 – invading adjacent structures

TNM Staging
- NX – not assessed
- N0 – no nodal involvement
- N1 – single, ipsilateral node, <3 cm
- N2 – nodal metastasis, 3-6 cm
- N2a – single, ipsilateral node, 3-6 cm
- N2b – multiple ipsilateral nodes, <6 cm
- N2c – bilateral or contralateral nodes, <6 cm
- N3 – nodal metastasis, >6 cm
TNM Staging

- MX – not assessed
- M0 – no distant metastasis
- M1 – distant metastasis

TNM Staging

<table>
<thead>
<tr>
<th>TNM</th>
<th>STAGE</th>
<th>5 YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0M0</td>
<td>Stage I</td>
<td>85%</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>Stage II</td>
<td>66%</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>Stage III</td>
<td>41%</td>
</tr>
<tr>
<td>T1-3N1M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any T4</td>
<td>Stage IV</td>
<td>9%</td>
</tr>
<tr>
<td>Any N2-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MY ORAL CANCER WAS DISCOVERED TOO LATE.
Management of Treatment Complications

Radiation Therapy

- Maximum treatment to tumor limited by unavoidable damage to normal tissue
- Damage directly proportional to volume of tissue irradiated and total radiation dose
- Damage inversely proportional to number of fractions given and total dosage time
Radiation Changes
- Radiation dermatitis
- Acute mucositis
- Osteoradionecrosis
- Xerostomia
- Loss of taste

Radiation Dermatitis
- Erythema
  - Tanning
  - Transient hair loss
Acute Mucositis

- Radiation dose outpaces regenerative ability of normal mucosa
  - 180 cGy(rad) per day, 5 days per week
- Appear 14 days following initiation of therapy
- May require interruption of therapy, nasogastric intubation or gastrostomy tube
Acute Mucositis

- Topical anesthetics
- Systemic analgesics (usually narcotic)
- Antimicrobial (usually antifungal) therapy
- Systemic anti-inflammatory therapy
From my good friend

Randy Mellard, DDS, MS
Osteoradionecrosis

- Higher risk in dentate patient
- Higher risk with post-therapy extraction
- Mandible >> maxilla
- Late complication (> 1 year post tx)
- Irreversible bone changes
- Focal sequestration progress to necrosis
- Intense pain
- Potential jaw fracture
Osteoradionecrosis

- Pre-therapy extraction of questionable teeth
- Antibiotics
- Hyperbaric oxygen
- Vascularized flaps
- Resection

Xerostomia

- Serous acini more sensitive
- Residual saliva, when present, is mucous
- Usually regenerates to some degree
  - May take up to 12 months
Xerostomia

- Variable therapy
  - Water
  - Artificial saliva
  - Sialogogues
  - Pilocarpine, cevimeline, bethanechol
Candidiasis

- Related to xerostomia
- Pseudomembranous or erythematous
- Better results with systemic therapy
  - Topical rinses ineffective
  - Difficulty in dissolving troches / tablets
- Lidocaine viscous
- Systemic analgesics
- Salivary stimulants or replacement
Loss of Taste

- Hypogeusia (partial loss of taste)
- Ageusia (complete loss of taste)
- Dysgeusia (altered taste)
- Usually regenerate within 4 months
- Zinc supplements (100 mg/day) helpful
Dental Caries

- Aggressive therapy
- Scrupulous oral hygiene
- Dietary alterations
- Chlorhexidine mouth rinses
- Topical fluoride
- Salivary stimulation
Dental Treatment Planning

- Anticipated bone dose
- Pre-therapy dental status
- Extraction techniques (primary closure)
- Extraction healing time before radiation (minimum 7-10 days)
- Patient compliance and motivation