Oral Cancer- 2007
Nelson L. Rhodus, DMD, MPH
Professor
Academy of Distinguished Professors

Director, Division of Oral Medicine
Diplomate, American Board of Oral Medicine
Faculty, Comprehensive Cancer Center
University of Minnesota

Member of the ADA: CAPIR

2003 - 2007

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
Member, Medical Advisory Board

A expert is someone who learns more and more about less and less until he knows everything about nothing.

Thanks!
Oral-pharyngeal squamous cell carcinoma

- Cancer of the mouth and pharynx accounts for nearly 40,000 cases of cancer per year in the U.S. and the sixth most common cancer worldwide.
- The 5-year survival rate from these carcinomas has not improved in the past 30 years (~50%)!

ORAL CANCER PREDISPOSING FACTORS

- Age (>95% = >40y.o.; mean ~60)
- Tobacco use (smoking or smokeless)
- Excessive ethanol intake
- Immunosuppression
- Systemic disease (syphilis, HIV, renal)
ORAL CANCER - epidemiology

- Average age at diagnosis = 63 y.o.
- 83% of Oral Cancer > 55 y.o.
- **New epidemiology: younger-50 yo F.**
- M: F > 2:1 (incidence and deaths)
- 2:1 mortality in African-Americans vs. Caucasians
- Peak in African-Americans 20 EARLIER
### ORAL CANCER

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>5000</td>
<td>28</td>
</tr>
<tr>
<td>Lip</td>
<td>4200</td>
<td>23</td>
</tr>
<tr>
<td>Salivary</td>
<td>2400</td>
<td>14</td>
</tr>
<tr>
<td>FOM</td>
<td>2300</td>
<td>13</td>
</tr>
<tr>
<td>Buccal</td>
<td>1500</td>
<td>9</td>
</tr>
<tr>
<td>Gingiva</td>
<td>1500</td>
<td>9</td>
</tr>
<tr>
<td>Palatal</td>
<td>900</td>
<td>6</td>
</tr>
</tbody>
</table>
### ORAL CANCER
(5-yr. survival by TNM)

<table>
<thead>
<tr>
<th>Site</th>
<th>Localized</th>
<th>Nodes</th>
<th>Metastasis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip</td>
<td>89</td>
<td>57</td>
<td>40</td>
<td>86</td>
</tr>
<tr>
<td>Tongue</td>
<td>52</td>
<td>22</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>FOM</td>
<td>65</td>
<td>31</td>
<td>14</td>
<td>44</td>
</tr>
<tr>
<td>Others</td>
<td>61</td>
<td>29</td>
<td>18</td>
<td>44</td>
</tr>
</tbody>
</table>

### Carcinoma of the tongue

- At the time of initial diagnosis, **50%** have already metastasized
- **35-40 %** will metastasize later
Carcinoma of the tongue

- At the time of initial diagnosis, 67% are already TNM=stage III or IV
- Overall 5-year survival rate <33%
ORAL CANCER
PREDISPOSING FACTORS

- Viruses (HPV, HIV, EBV, HSV)
- chronic inflammation or trauma
- HCV, liver disease
- Post-solid organ transplants
- nutritional deficiencies
- A+B+C+D…..

ORAL CANCER
DETECTION

- INSPECTION
- PALPATION
- Normal anatomy vs. deviations

“Dans les champs de l’observation le hastard ne favorise que les esprits préparés”

L. Pasteur, 1854
ORAL CANCER
DETECTION
• In the past 40 years the 5-yr. survival rate from OSCCa has not improved! ( <50 %)
• EARLY DETECTION (asymptomatic)
• 75 % are EASILY CLINICALLY VISUALIZED
• >90 % CURE RATE if EARLY !!
• Mistaken for benign lesions
• Lost to follow-up
Squamous cell carcinoma

CLINICAL APPEARANCE

• COMBINATIONS and ±
• COLORS and MORPHOLoGY
• Smooth or granular, elevated, ulcerated and plaques, fissuring (or not), bleeding (or not), indurated (or not), NOT symptomatic
ORAL CANCER

- CLINICAL APPEARANCE
- 33% = ERYTHROPLAKIA
- 60% = MIXED
- 5% = WHITE
ORAL CANCER DETECTION

- Thorough, comprehensive head and neck and intraoral soft tissue examination on ALL patients
- Suspicion to r/o Ca for ALL lesions
- Follow-up, periodic examination at least each recall (6 mos.)

ORAL CANCER DETECTION

- Comprehensive head and neck and intraoral soft tissue examination takes <5 minutes!
ORAL CANCER

• BIOPSIES
• if SMALL (exophytic, other) LESIONS ... COMPLETE EXCISION
• if LARGE (plaques, tumors) LESIONS ... INCISIONAL BIOPSY
  “high yield” zones
  avoid ulcers-necrotic areas
  normal tissue margins
Leukoplakia to SCCA

- time to transformation = 7.2 years
- precedent dysplasia= 17-34 %
- NY = 16 % WITH Bx-proven dysplasia >>> SCCA in 3 yrs.
- MN= 42 %WITH Bx-proven dysplasia >>> SCCA in 3 yrs.
- mean age 63;  F = M

ORAL DYSPLASIA and ORAL CANCER

- 141 specimens with “dysplasia”
- 108 DDS said they “followed-up” = 76.5 %
- 20 were biopsied on follow-up = 14. 1%
- 16 lesions became cancer *= 11.3%
- 42. 8 % of severe dysplasias became cancer !!!

  - only 7/20 were diagnosed on second biopsy
  - Only 2 of the 9 severe dysplasias which became cancer
ORAL CANCER DETECTION

• CLINICAL vs. DEFINITIVE DIAGNOSIS

• History
• Contributing factors
• Clinical appearance  
  SITE-COLOR-MORPHOLOGY
• General medical

Diagnostic Protocol
Chemiluminescence

- Normal epithelium absorbs ViziLite illumination and appears dark
- Abnormal epithelium reflects ViziLite illumination and appears white
TBlue$^{630}$ Stained Lesion

**Before:** Lesion is difficult to see and define

**After:** Lesion is easy to view, document and evaluate. Measure the stained lesion and document the staining pattern

Fluorescent Visualization (FV)
Tissue Fluorescence

Light (Excitation Source) → Reflection (Scattering) → Fluorescence → Detector (Eye) → Filter

1st Patient

Loss of Fluorescence Visualization (FV) = (Positive Response)

Clinical Appearance (Visible White Light)

Carcinoma-In-Situ (CIS)

Toluidine Blue Stain

Fluorescent Visualization (FV)

Copyright © 2002-2003 by Oral Health Study, Oral Oncology/Dentistry, BCCA.
Transepithelial cytology

Oral CDx ® ("brush biopsy")

- some, limited clinical diagnostic value (decide to Bx)
- irregular epithelial cells (not flat)
- enlarged, irregular size
- and shape of nuclei
- hyperchromatic nuclei
Oral-pharyngeal squamous cell carcinoma

- Over 90% of these oral-pharyngeal cancers are squamous cell carcinoma (SCCa).
- Most lesions are easily seen in the oral cavity.
- >75% cure rate if diagnosed in early stages.

Most of these carcinomas are preceded by chronic inflammatory (preneoplastic) oral lesions or epithelial dysplasia—leukoplakia. Malignant transformation rate = 5-17% w/i 8 years (Silverman, 1992).

Oral carcinogenesis is a multi-step process:

- Cell Differentiation
- Cell Proliferation
- Benign Squamous Hyperplasia LOH 31%
- Oncogenes Allele Loss Gene mutations
- Intraepithelial Neoplasia/CIS Oral SCCa LOH 97%
- Tumor Suppressors
- Terminal Differentiation → Apoptosis
- Angiogenesis

LOH 67%
Hypothesis- Will NF Kappa B p65 enrichment upregulate squamous carcinogenic phenotype?
What is mechanism of proliferative increase?

Figure 6. Effect of NFκB promoter site mutation on CD1 promoter activity in rhek-p65 cells. Reporter plasmid that contained a mutagenized NFκB site were transfected into rhek-p65 cells. Luciferase activity was quantified as relative light units normalized to β-galactosidase activity. RLU, relative light units. Values are means ± SEM.
Rhek p65 Cell IL-8 Production

Increase of luciferase activity by non-inducible overexpression of NFkB in rhek-p65 cells. The IL-8 reporter plasmid containing the 133bp promoter fragment with wild-type sequence was transfected into rhek-p65 cells. Values are means SEM. polyclonal/p65 cells, 1.07 ± 0.2 compared with its control, 0.39 ± 0.06, p< 0.0157

Figure 14. IL-8 secretion in rhek-p65 cells. The quantity of IL-8 secreted was measured by ELISA. Values are means SEM

Is NF Kappa B the Maestro of this orchestrated process?
Oral Preneoplasia Initiative

• Translational Research on Oral Carcinogenesis
• Focus is precancer biomarker discovery, validation, application, experimental preclinical therapeutics affecting NF Kappa B dependent genes, PPAR gamma activation, or both; gene expression, candidate pathways; proteomics
• Goal is to move drugs and hypothesis driven intermediate endpoints into early phase clinical trials, primarily in leukoplakia (epithelial dysplasia)

Inflammation, NF Kappa B, and Oral Cancer: Back and Forth from the Bench to the Clinic
NF κ B

- Transcription factor
- Early response gene
- Inactive in normal cells as I κ B
- Found in cytoplasm, when activated translocates to nucleus as a heterodimer of p50 and p65, then transcribes several proinflammatory, proangiogenic proteins
- Stress activated (hypoxia, etc.)
- Elevated in tobacco use, chronic inflammatory conditions, et.al.
Inflammation, NF Kappa B,

**Effects on Cancer Cells**

- Cell cycle (G₀, G₁)
- Differentiation (keratins CK4, cell-cell interaction)
- Angiogenesis (VEFG, Factor VIII, TGF-B)
- Oncogenes (ras, myc, bcl-2)
- Tumor suppressors (p53, p16, p21)
- Transcription factors (AP-1)
- Programmed Cell Death (caspase)
- Immunological control (NK cells)
- Oncogenic Pathogens
The cause of cancer is from one swallowing small amounts of one’s own spit over years and years
Utility of **saliva** as a surrogate diagnostic indicator

- Diagnosis of squamous cell carcinoma
- Carcinogenic progression of preneoplastic oral lesions
- Prognostic indicator
- Monitor efficacy of chemoprevention

16 biomarkers

NF-κB dependent cytokine levels in saliva of patients with oral preneoplastic lesions and oral squamous cell carcinoma

Nelson L, Rhodus DMD, MPH	extsuperscript{a,b}, Vu Ho MD	extsuperscript{b}, Craig S. Miller DMD, MS	extsuperscript{c}, Sandra Myers DMD, MS	extsuperscript{a}, Frank Ondrey MD, PhD	extsuperscript{b}

- TNF α, IL-1 α, IL-6, IL-8 in the local oral milieu (i.e. SALIVA) may play an important role in angiogenesis and the progression of neck squamous cell carcinoma in chronic inflammatory lesions
Oral cancer Microarray Project

- Compare gene expression profiles of patients with oral preneoplasia and oral cancer to normal controls
  - Identify differential gene expression profiles using freshly biopsied tissues and cytological smears
- Identify candidate pathways involved in the disease process

Clustering of 2891 Differentially Expressed Genes

- MOST INTERESTING = LOSS OF IMMUNOPROTECTIVE FUNCTIONAL PATHWAYS
  - UPREGULATED GENE PRODUCTS:
    - VEGF, VEGF 165 RECEPTOR 2
    - FIBROBLAST ACTIVATION PROTEIN
    - PLATELET-DERIVED ENDOTHELIAL CELL GROWTH FACTOR
    - TRAIL RECEPTOR 2
    - RIP PROTEIN KINASE
    - P CADHEDRIN, OB CADHEDRIN-2, OB CADHEDRIN-3
    - CYCLIN DEPENDENT KINASE 4, CYCLIN A
    - MAP KINASE ACTIVATED PROTEIN KINASE -2
Oral Cancer Microenvironment

Carcinogens

Chronic Irritation

Proinflammatory cytokines

Re Dox

ROS

Antioxidant depletion

QuickTime™ and a decompressor are needed to see this picture.

Oral Cancer Microenvironment

Carcinogens

Chronic Irritation

Proinflammatory cytokines

Re Dox

ROS
“Excuse me, may I be excused? My brain is full.”
Time to stop!