Oral Cancer: A Comprehensive Overview

Samip N. Patel, MD, FACS
Trevor Hartman, MD, FACS
Ricardo Padilla, DDS

Definition of Oral Cancer

Types of Oral Cancer

- Squamous Cell Carcinoma
- Metastases to the Mouth
- Salivary Gland
- Lymphomas and Leukemias
- Sarcomas (bone or soft tissues)
- Odontogenic
- Other Malignancies

Squamous Cell Carcinoma

- Neoplastic keratinocytes from the surface epithelium invade adjacent areas and have metastatic potential
- Sites: Lateral and ventral "oral" tongue
- Sites: Buccal mucosa, gingiva, hard palate, soft palate
- Types of epithelium
  - Keratinizing epithelium
  - Non-keratinizing epithelium
  - Reticulated epithelium
  - Drop-down carcinoma
  - Superficially invasive OSCC
  - Multifocal keratocystic odontogenic

Oral Squamous Cell Carcinoma

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Risk Factors for Oral Cancer

- Tobacco in all forms
- Excessive alcohol
- High-risk Human Papillomavirus
- Immunosuppression or immunodeficiency
- Betel quid and gutka
- Actinic damage (lip vermilion)
- Gender
- Age
- Poor nutrition
- HIV
- Genetic conditions (Fanconi anemia, Dyskeratosis congenita, Field cancerization)
- Lichen planus and PVL

Precancerous and Early Cancerous Oral Lesions

- Precancerous Oral Lesions
  - Implies known potential for malignant transformation
  - Warrants pre-emptive action/close observation
  - Cannot predict
  - High level of vigilance required
Actinic Cheilitis (Sailor’s Lip; Solar Cheilitis Type of actinic keratosis - 6-10% transformation rate)

- Lower Lip
- White men > 40 yoa
- Vermilion - atrophic, pale, glossy surface, loss of demarcation at border
- —> Fissuring and ulceration with crusting and scaling

Actinic Cheilitis (Sailor’s Lip; Solar Cheilitis)

- Biopsy
- Excision
- Topical 5-FU
- Prophylactic laser ablation/vermilionectomy
- Close long-term followup
Leukoplakia

- "White Patch" - asymptomatic
- White plaque that cannot be rubbed off
- Should be biopsied - up to 20% may exhibit dysplasia or carcinoma
- Most prove to be hyperkeratosis or chronic inflammation
- Ventral/lateral tongue and floor of mouth

Leukoplakia

Proliferative Verrucous Leukoplakia

- Very high rate of malignant change
- Thick, exophytic (flat in early stages)
- Buccal mucosa and gingiva
- Women > 50 yoa
- Slow growing, multifocal
- TOC - Surgical resection
Proliferative Verrucous Leukoplakia

Tobacco Pouch Keratosis

- Direct effect of smokeless tobacco, form of leukoplakia
- Lesions occur at site of contact
- Mandibular anterior labial vestibule
- Buccal vestibule
- Mucosa - gray to white, wrinkled, pouch like depression, leathery
- Lower risk than conventional leukoplakia
Oral Submucous Fibrosis
- Chronic inflammation, atrophy, fibrosis
- Betel product
- Trismus
- 4-13% malignant transformation rate

Erythroplakia
- “Flat red area”
- Bright red, velvety appearance
- Asymptomatic
- 80-90% incidence of severe dysplasia or carcinoma
- Biopsy mandatory
Erythroplakia

Oral Lichen Planus

- Chronic mucocutaneous T cell-mediated inflammatory condition
- 1% of adult population
- Women > men
- Idiopathic
- Reticular, Erythematous, Erosive
Early Oral Cancers

- Early detection directly results in improved survival
- Tobacco use and habitual alcohol consumption synergistically increase risk of developing oral carcinoma
- Oral cavity is unlike other anatomic regions of upper aerodigestive tract — routine detection of early lesions is possible
- Delay in diagnosis can still occur

Early Oral Cancers

- 14% of all head and neck cancers
- Mean age of presentation 64 yoa
- Male predominance (60%)
- SCC - 86.3%
- Adenocarcinoma - 5.9%
- Verrucous carcinoma - 2%
- Lymphoma - 1.5%
- Kaposi Sarcoma - 1.5%

Early Oral Cancers

- At time of diagnosis -55% of pts have early stage lesions (stages I and II)
Presentation of Advanced Disease and Metastasis

Subsites

• Lips
• Alveolar Ridge
• Oral Tongue
• Retromolar Trigone
• Floor of Mouth
• Buccal Mucosa
• Hard Palate
Subsites

- changes in fit of dentures
- dysphagia
- pain
- ulcers
- otalgia
- trismus
- bleeding
- halitosis
- weight loss
- odynophagia
- dysarthria
- facial numbness

Advanced Disease
Diagnostic and Staging Process

Diagnosis
- History and Physical Exam
- Dyes/Laser
  - Toluidine Blue, chemoluminescence, Spectroscopy, Laser
- Biopsy
  - FNA, Brush, Incisional, Excisional
  - Sentinel Node Biopsy

History and Physical Exam
- EARLY
  - Non-healing ulcer
  - white/RED
  - Otalgia - ear pain
  - Tooth mobility
  - Bleeding
  - Swelling
  - Oral pain
- LATE
  - Oral numbness
  - Tongue weakness
  - Trismus
  - Adenopathy
  - Changes to speech
  - Changes to swallowing
  - Airway Obstruction
Role of Screening Tests

<table>
<thead>
<tr>
<th>Table 1: The various diagnostic modalities for oral cancer detection</th>
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<tbody>
<tr>
<td>Visual examination</td>
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<tr>
<td>Excision biopsy and Histopathology</td>
</tr>
<tr>
<td>Oral mucosal biopsy (OralCOV)</td>
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<tr>
<td>Toluidine blue</td>
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<tr>
<td>Light-based detection systems</td>
</tr>
<tr>
<td>ChromaKonkurrence (Visi6Plus, Micro6LD, Orascoptic-DK)</td>
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<tr>
<td>Tissue fluorescence spectroscopy</td>
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<tr>
<td>Biomarkers</td>
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<tr>
<td>DNA analysis</td>
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<tr>
<td>Laser capture microdissection</td>
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Utility of Screening Tests

<table>
<thead>
<tr>
<th>Table 2: Comparison of Toluidine Blue Lysate with Microscopic Diagnosis</th>
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<tbody>
<tr>
<td>Biopsy Diagnosis</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Carcinoma</td>
</tr>
<tr>
<td>Dysplasia</td>
</tr>
<tr>
<td>Benign</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Toluidine blue (lysate) staining is a useful adjunct to histological examination and biopsy. The mechanism is based on selective binding of the dye to dysplastic or malignant cells in the epithelial layer. It may be that toluidine blue selectively stains for a third component and this third component is DNAs, which is increased in neoplastic cells.

Toluidine blue has been recommended for use as a mouthwash or for direct application to suspicious lesions. Its mechanism of action is based on its ability to stain keratinocytes and abnormal epithelial tissue. In addition, it can help to identify the most appropriate biopsy sites for histological examination.

Light-based laser

- Vizilite Plus, VELscope, ORascoptic DK
  - Commercially available, but not covered by insurance
  - Most common in dental practices
  - Abnormal tissue (structure or metabolic) will show unique absorbance & reflective properties
  - No evidence of efficacy
  - Not “diagnostic test” - no S&S

Only a definitive test examining cells or tissue can determine the biologic behavior of a lesion.
Brush Biopsy

- OralCDx - oral brush biopsy with computer assisted analysis
- identifies dysplasia in areas without suspicion
- Exfoliative cytology from full thickness mucosa - painless
- Most results benign
- Perhaps guides what should be biopsied

Standard of Care Biopsy

- Incisional biopsy
  - preferred
  - allows to plan definitive surgery
  - include submucosa
- Excisional biopsy
  - Take a visible grossly normal margin
  - Consider frozen section
  - positive margins on permanent complicates management
Diagnostic Imaging

- CT Neck/Chest (contrasted)
- Gold standard for staging
- Bone invasion
- PET/CT - Metabolic FDG-avidity
- Post treatment “Advanced disease”
- Utility in setting of dental artifact
- MRI
  - Excellent soft tissue definition
  - Delineate tumor from normal tissue
  - ISSUE - Metal Artifact
  - Nerve involvement
  - Mental (Bone), Lingual (Tongue)

Staging

AJCC 8th Primary Site Stage

- T1: Tumor ≤ 4 cm, deep invasion ≤ 5 mm, no lymph node involvement
- T2: Tumor > 4 cm or depth of invasion > 5 mm, or lymph node involvement
- T3: Tumor invades bone, cartilage, muscle, or major vessel
- T4: Tumor invades nervous system, pericardium, or main body cavity structures

- N0: No lymph node involvement
- N1: 1-3 lymph nodes involved
- N2: 4-6 lymph nodes involved
- N3: 7 or more lymph nodes involved

- M0: No distant metastasis
- M1: Distant metastasis

DOI

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Nodal Staging

<table>
<thead>
<tr>
<th>N</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≥5 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, &lt;5 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
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Overall AJCC Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1, T2</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td>IV</td>
<td>T3</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>V</td>
<td>T4</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>VI</td>
<td>Any T</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>VII</td>
<td>T1b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>VIII</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Treatment Options for Oral Cancer
Primary Therapies

- Destruction - CO2 laser ablation
  - dysplasia / cis - NOT invasive SCCA
- Excision
  - Gold Standard - 5-10 mm margins
- Radiation Therapy
  - Palliative or no surgical option
- Multimodal
  - Surgery with adjuvant CRT
  - Advanced stage

Excision

- Gold Standard
- Various excision tools
  - Knife > laser > cautery (margin preservation)
  - Estimate 5-10 mm margin for resection
  - Grossly normal can be abnormal histologic/molecular
  - Frozen section margins advised
  - Toluidine blue or NB (fluorescence)
- TLM, open composite resection
- Reconstruction
  - >1/3 tongue, significant FOM defect (swallowing)
  - >1/2 bucal (trismus), bone exposure/removal

Treatment of Bone

- Obvious Invasion
  - Nerve enhancement MRI / Gross cortical erosion on CT
  - Segmental Mandibulectomy
  - Maxillectomy
  - Osteoradionor
  - Flap reconstruction
- Cancer abutting mandible
  - Marginal Mandibulectomy
  - Consider Staging Neck
  - Primary Closure
  - Flap Reconstruction
    - FOM and TONGUE resection
**Regional Treatment**

- Risk of occult nodal metastasis
  - DOI ≥ 4 mm
  - Primary cancer ≥ T2 (2.1 cm)
  - 20% risk indicates need for neck dissection
- Levels dissected
  - FOM/Oral tongue - levels 1-4
  - MRND/SND - sparing SCM/IV/CNIX
  - Risk - CN VII, XI & XII injury, vessel trauma

**Sentinel Node Dissection**

- Nodal micrometastases in up to 50%
- First sentinel node 1996
- Multiple sentinel nodes possible
- Promising, but unproven

**Adjuvant Radiation Therapy**

- Primary Site
  - T3 or T4 cancer
  - Perineural Invasion
  - Lymphovascular space invasion
  - Positive Margins
- Lymph nodes
  - Nodal Involvement (2 or more)
  - Extranodal Extension
  - What about Chemotherapy ??????
Adjuvant Chemoradiation Therapy

In patients with LA SCCaN undergoing definitive surgery (stages III, IVa), local and regional recurrence rates remain significant (up to 50% at 2 years), distant metastases develop (up to 20% at 2 years), and 5-year survival rates are poor. Postoperative adjuvant RT in this setting has been used in patients with pathologic findings associated with high risk for inguinal recurrence.

To improve outcomes, the role of concurrent administration of epirubicin chemotherapy during RT has been investigated in two phase III clinical trials, where high-dose cisplatin (100 mg/m²) administered on days 1, 22, and 43 of concurrent RT was evaluated.

High Risk Features

- **Absolute Indications for chemotherapy**
  - Positive Margins
  - Extracranial Extension
  - Extracranial Extension consensus recommendation: “This subgroup of patients at high risk for recurrence, and addition of chemotherapy to adjuvant RT represents the current standard of care.” endorsed by National Comprehensive Cancer Network (NCCN)

- **Other Indications to consider**
  - pT3 / pT4, PNI, LVSI
  - N2 or N3 disease, levels IV/V involvement
Prognostic Factors of OHNC

Demographic Prognostic Factors

- Female Sex
- Age > 40
  - Increasing incidence in SCCA patients < 40 yrs old in US.
- Systemic Illness
  - Autoimmune Disease
  - Tobacco and EtOH
    - Greater likelihood of health problems in alcoholics
    - Any tobacco during RMT (OR decrease 74% to 45%)
  - Southeast Asian, African Americans
  - Non-vegetarian - nitrosamines vs antioxidants

Surgical Prognostic Factors

- Positive Margins
- Lymphovascular space invasion
  - predicts nodal mets and distant recurrence
- Perineural invasion - 50% of specimen
  - predictor locoregional recurrence & nodal mets
- Nodal Metastasis
  - More than 2 nodal groups
  - Extracapsular Invasion
- FOM / soft palate / posterior tongue
  - Tumor > 2 cm, DOI > 5 mm, volume > 6 cm³
Molecular Prognostic Factors

- p53 mutations
  - 2.4 fold increased locoregional recurrence
- Angiogenesis Related Factor (VEGF)
- MVD correlates with risk of nodal mets
- Cyclin D
  - Primary positive – 4x increased risk occult nodal mets
- EGF - epidermal growth factor receptor
  - overexpression - poor prognosis & radio resistance
- LOH
- Cytokeratin 8/18
  - decreased overall and progression free survival
- HPV – prognostic in men only


Other Prognostic Factors

- Distance to treatment
- Time to Treatment Initiation
  - Increased risk of death > 45 days
- Socioeconomic status
- Marital Status
- Treatment Center
  - Academic > Community Cancer Hospital > Community Hospital


Oral Complications after Oral Cancer Treatment

- Xerostomia
- Opportunistic infections
- Mucoitis
- Caries
- Periodontal disease
- Trismus
- Fibrosis
- Pain
- Ageusia
- Osteoradionecrosis
  - Medication-related osteoradionecrosis of the jaws
Xerostomia
(salivary hypofunction, sticky saliva, dryness)

- Hydration: Don’t sip water, chug it down
- Lubrication: Rinse with edible oil prn

Candidiasis
(match medicine to patient)

Oral Mucositis
Dose-dependent (XRT-related in this case)
Radiation Dental Caries
(Dental evaluation before start of treatment)

Medication-related osteonecrosis of the jaws
(Multiple agents are involved now)

MRONJ

Risk factors
- Type of agent and dose/route
- Comorbidities (diabetes, smoking, RA, dialysis, anemia, osteomalacia, hypoxia, low perfusion)
- Microtrauma to alveolar bone and gingiva
- Oral hygiene and oral flora management
- Others