Keratinizing Dysplasia and Select Variants of Head & Neck Squamous Cell Carcinoma

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Moffitt Cancer Center
Tampa, FL

Head & Neck Squamous Cell Lesions
Outline

- Keratinizing Dysplasia
- Select Variants of Squamous cell carcinoma

Normal Squamous Epithelium

Vocal cord
Floor of Mouth
Buccal Mucosa
Oral Leukoplakia

Vocal Cord Leukoplakia

Laryngeal Speckled Leukoplakia
Epithelial Alterations
Histopathology

- (Hyper)keratosis
- Hyperplasia
- Dysplasia:
  - Spectrum of architectural and cytological epithelial changes caused by a gradual accumulation of genetic changes with an increased likelihood of progression to squamous cell carcinoma

Criteria for Dysplasia
2017 WHO Blue Book

<table>
<thead>
<tr>
<th>Architectural changes</th>
<th>Cytological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>irregular epithelial stratification</td>
<td>Abnormal variation in nuclear size</td>
</tr>
<tr>
<td>loss of polarity of basal cells</td>
<td>Abnormal variation in nuclear shape</td>
</tr>
<tr>
<td>Group-shaped rete ridges</td>
<td>Abnormal variation in cell size</td>
</tr>
<tr>
<td>increased number of mitotic figures</td>
<td>Abnormal variation in cell shape</td>
</tr>
<tr>
<td>Abnormally suprabasal mitotic figure</td>
<td>Increased N/C ratio</td>
</tr>
<tr>
<td>Premature keratinization in single cells</td>
<td>Abnormal mitotic figures</td>
</tr>
<tr>
<td>Keratin pearls within rete ridges</td>
<td>Increased number and size of nuclei</td>
</tr>
<tr>
<td>loss of epithelial cell cohesion</td>
<td>Hyperchromasia</td>
</tr>
</tbody>
</table>

Dyskeratosis

- Keratin not on the surface
- Individual cell keratinization
- Keratin pearl(s) in the middle or lower half of the epithelium
- Pink or glassy cytoplasm
- Paradoxical maturation
Dyskeratosis

Paradoxical Maturation

Keratosis without Dysplasia
Verrucoid/Papillary Keratosis without Dysplasia

(Papillary or verrucoid) Keratosis without Dysplasia

Upper Aerodigestive Tract Epithelial Dysplasia

• “Classic” or Non-Keratinizing:
  – Mild dysplasia
  – Moderate dysplasia
  – Severe dysplasia = Carcinoma in situ (CIS) full thickness intraepithelial dysplasia
CIS (Nonkeratinizing)

- Uncommon as isolated lesion in H&N
- Occurs in mucosal sites that are usually clinically quiescent (e.g., supraglottic larynx, oro- & nasopharynx) only seen in association with invasive SCC

Upper Aerodigestive Tract
Epithelial Dysplasia

- Keratinizing >>>> Nonkeratinizing:
  - Mild dysplasia
  - Moderate dysplasia
  - Severe dysplasia

Keratinizing Mild Dysplasia
Keratinizing Moderate Dysplasia

Keratinizing Severe Dysplasia

Moderate? Severe? CIS?
“Drop Off” Carcinoma

Carcinoma In Situ (CIS)

• In the absence of full thickness intra-epithelial dysplasia is the use of CIS justified?
• Does keratinizing severe dysplasia = CIS?
• Is it important to separate moderate and severe dysplasia/CIS?

Upper Aerodigestive Tract
Keratinizing Dysplasia

• Goal of any grading system is:
  – Reproducible and Applicable
  – Convey to the clinician the potential risk for progression of disease
Upper Aerodigestive Tract
Grading Keratinizing Dysplasia

- Imprecise and subjective
- Preferred grading based on degree and extent of cellular and maturation alterations
  - mild dysplasia
  - moderate dysplasia
  - severe dysplasia

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Incidence of Invasive Carcinoma Developing in Patients with Keratosis Without Atypia

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>Total number of cases</th>
<th>Number of invasive carcinomas</th>
<th>% of all cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGavan (1960)</td>
<td>66</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Norris (1963)</td>
<td>30</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Gabriel (1973)</td>
<td>50</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Henry (1979)</td>
<td>29</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>Crissman (1979)</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hellquist (1982)</td>
<td>98*</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gillis (1983)</td>
<td>7</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>Kalter (1987)</td>
<td>38</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Silamukka (1989)</td>
<td>604</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Hoijst (1989)</td>
<td>128*</td>
<td>6</td>
<td>4.7</td>
</tr>
<tr>
<td>Blackwell (1995)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1106</strong></td>
<td><strong>36 (3.3%)</strong></td>
<td><strong>5.25 (average)</strong></td>
</tr>
</tbody>
</table>

*Includes some patients with mild atypia.
Source: Sec. IX, Refs. 1-4, 7, 9-14.

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Incidence of Invasive Carcinoma Developing in Patients with Keratosis with Atypia

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<th>% of all cases</th>
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<tbody>
<tr>
<td>McGavan (1960)</td>
<td>18</td>
<td>2</td>
<td>11.1</td>
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<tr>
<td>Norris (1963)</td>
<td>86</td>
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<td>5.8</td>
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<tr>
<td>Gabriel (1973)</td>
<td>55</td>
<td>4</td>
<td>7.3</td>
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<tr>
<td>Henry (1979)</td>
<td>14</td>
<td>3</td>
<td>21.4</td>
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<tr>
<td>Crissman (1979)</td>
<td>42</td>
<td>3</td>
<td>7.1</td>
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<tr>
<td>Hellquist (1982)</td>
<td>63*</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Gillis (1983)</td>
<td>17</td>
<td>5</td>
<td>29.4</td>
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<tr>
<td>Kalter (1987)</td>
<td>92</td>
<td>20</td>
<td>21.7</td>
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<tr>
<td>Silamukka (1989)</td>
<td>317</td>
<td>44</td>
<td>13.9</td>
</tr>
<tr>
<td>Hoijst (1989)</td>
<td>19</td>
<td>8</td>
<td>42.1</td>
</tr>
<tr>
<td>Blackwell (1995)</td>
<td>50</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>773</strong></td>
<td><strong>118 (15.3%)</strong></td>
<td><strong>18.4 (average)</strong></td>
</tr>
</tbody>
</table>

*Includes only grade II and III atypia
Source: Sec. IX, Refs. 1-4, 7, 9-14.
Grading Keratinizing Dysplasia

- No statistical difference in progression to invasive SCC between keratinizing moderate dysplasia and keratinizing severe dysplasia/CIS
- Justification to 2-Tier grading scheme:
  - Low-grade Dysplasia = Mild dysplasia
  - High-grade Dysplasia = Moderate Dysplasia, Severe Dysplasia, CIS
- Better reproducibility

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>Mild (Cases)</th>
<th>Moderate (Cases)</th>
<th>Severe (Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halaban (1982)</td>
<td>5.86*</td>
<td>3.24</td>
<td>9.17*</td>
</tr>
<tr>
<td>Silvainuka (1989)</td>
<td>2.05</td>
<td>2.23</td>
<td>25.90</td>
</tr>
<tr>
<td>Hupel (1999)</td>
<td>2.23*</td>
<td>4.90</td>
<td>4.90</td>
</tr>
<tr>
<td>Blackwell (1999)</td>
<td>1.26</td>
<td>5.15</td>
<td>4.19</td>
</tr>
<tr>
<td>Total</td>
<td>26.49%</td>
<td>16.75%</td>
<td>42.46%</td>
</tr>
</tbody>
</table>

*Includes some cases of keratinization atypia
*Includes some cases of carcinoma in situ

Source: Nat. Hist. Mol. 2; 0, 13, 0.

Binary Grading – Laryngeal Dysplasia

2017 WHO Blue Book

<table>
<thead>
<tr>
<th>Level of abnormal proliferation (WHO 2015)</th>
<th>WHO 2015</th>
<th>SIN classification (90)</th>
<th>Ljubljana classification (79)</th>
<th>Amended Ljubljana classification (79)</th>
<th>WHO 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower 1/3</td>
<td>Normal squamous epithelium</td>
<td>Squamous hyperplasia</td>
<td>Squamous hyperplasia</td>
<td>Low-grade SIL</td>
<td>Low-grade dysplasia</td>
</tr>
<tr>
<td>1/3 to 2/3</td>
<td>Mild dysplasia</td>
<td>SIN 1</td>
<td>Basaloid hyperplasia</td>
<td>Basaloid hyperplasia</td>
<td>Basaloid hyperplasia</td>
</tr>
<tr>
<td>2/3 to 1/3</td>
<td>Moderate dysplasia</td>
<td>SIN 2 or SIN 3</td>
<td>Apical hyperplasia</td>
<td>Apical hyperplasia</td>
<td>Apical hyperplasia</td>
</tr>
<tr>
<td>Upper 1/2 to 3/4</td>
<td>Moderate dysplasia</td>
<td>SIN 3</td>
<td>High-grade SIL</td>
<td>High-grade SIL</td>
<td>High-grade SIL</td>
</tr>
<tr>
<td>Full thickness</td>
<td>Severe dysplasia</td>
<td>SIN 4</td>
<td>Carcinoma in situ</td>
<td>Carcinoma in situ</td>
<td>Carcinoma in situ</td>
</tr>
</tbody>
</table>

*In a few selected centers, papilloma in situ is separated from high-grade dysplasia.
SIN, squamous intraepithelial neoplasia.
**Binary Grading – Oral Dysplasia**
*2017 WHO Blue Book*

<table>
<thead>
<tr>
<th>WHO dysplasia grade</th>
<th>Binary system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dysplasia</td>
<td>Low-grade dysplasia</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>High-grade dysplasia</td>
</tr>
</tbody>
</table>

- The cut-off point between low-grade and high-grade dysplasia, as suggested by Kajen C et al. (1991), is four architectural and five cytological changes (see Table 4.2), irrespective of the level within the epithelium.
- According to Naknaree P et al. (1972), a cut-off point of four architectural and four cytological changes may improve discrimination.

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**Keratinizing Dysplasia**

**Etiology**
- Tobacco (smoking, chewing)
- Alcohol
- Areca nut, with or without tobacco, causes oral submucous fibrosis with a relatively high frequency of oral dysplasia
- High risk human papillomavirus? Generally not considered a risk factor

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**Keratinizing Dysplasia**

**IHC Staining**
- **p16, p53 and Ki67 (MIB1):**
  - p16 of limited diagnostic utility in keratinizing dysplasias of the UADT
  - p53: increase expression
  - Ki67: increase intraepithelial proliferation rate through all epithelial layers
- Overall of limited utility
High-Grade Keratinizing Dysplasia

Oral Dysplasia and HR-HPV

- HR-HPV infection found in oral keratinizing dysplasias*
  - Majority clinically oral leukoplakias
  - Most adult men; Ventral tongue & FOM
  - Diffuse loss of squamous differentiation with karyorrhexis & apoptosis, brightly eosinophilic apoptotic cells throughout epithelium, and conventional dysplastic changes
  - ↑↑ proliferation index throughout epithelial layers
  - p16+IHC & high-risk HPV subtypes


HR-HPV FOM Dysplasia
HNSCC
Factors Associated with Prognosis

- Adequacy of resection (surgical margins)
- Pattern of invasion: cohesive vs dyscohesive
- Tumor size, depth of invasion (DOI), location
- LVI, neurotropism and soft tissue invasion
- Regional metastasis - Extranodal Extension
- Distant metastasis
- Angiogenesis; Host immune response
- Second malignancy

Depth of Invasion (DOI)

• T1: Tumor ≤ 2cm & DOI ≤5mm
• T2: Tumor ≤ 2cm & DOI >5mm & ≤10mm or tumor >2cm but not ≤4cm, & DOI ≤10mm
• T3: Tumor >4cm or any tumor DOI >10mm

Extranodal Extension
Variants of Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Squamous Cell Carcinoma Variants

- Verrucous Carcinoma
- Viral-Associated Carcinomas (HPV; EBV)
- Spindle Cell Squamous Carcinoma
- Papillary (Exophytic) SCC
- Basaloid Squamous Cell Carcinoma
- Adenosquamous Carcinoma
- Lymphoepithelial-like Carcinoma
- Adenoid SCC (angiosarcoma-like or acantholytic)
- Other variants:
  - NUT carcinoma
  - SMARCB1 (INI-1) Deficient Carcinoma

Verrucous Carcinoma (VC)

- Highly differentiated variant of squamous cell carcinoma with locally destructive but not metastatic capabilities
Verrucous Carcinoma

Clinical Features

- M > F; generally occurs in older age groups (6th – 7th decades of life)
- Sites:
  - oral cavity (4%) > larynx (1-3%) > other (sinonasal tract; nasopharynx)
- Symptoms vary according to site

Verrucous Carcinoma

Etiology

- Tobacco (smoking, chewing) use
- HPV may play an active role in the multistep progression to cancer by binding (via protein products) to the RB gene product removing regulatory block in the cell cycle (Science 1989;243:934-7)
- Recent studies using highly sensitive and specific molecular methods suggest that VC is not associated with human papillomavirus infection
Hybrid Carcinoma

- Tumor showing mixed histology including verrucous carcinoma and conventional SCC
- Oral cavity > larynx >>> other sites
- Biologic risk that of conventional SCC
  - potential for metastasis
- Treatment that of conventional SCC
Hybrid Carcinoma vs VC with Dysplasia or Minimal Invasion

  - VC (n=18)
  - VC with dysplasia or minimal invasion (VCDMI) (n=26) ≤ 2 mm
  - VC & SCC (n=14) >2 mm depth of invasion

- Prognosis:
  - VC or VCDMI: limited recurrences, no metastases, no deaths
  - VC&SCC: 50% recurrence; 14% nodal metastases; 36% DOD
Biopsy Diagnosis of Verrucoid Lesions

Biopsy Diagnosis of Verrucoid Lesions

Biopsy Diagnosis of Verrucoid Lesions
Biopsy Diagnosis of Verrucoid Lesions

Verrucous Carcinoma
Biopsy Diagnosis

- Biopsy diagnosis of VC extremely difficult
- Adequate material is critical to interpretation and should include ample epithelial-stromal interface:
  - Pathologists should not over interpret a verrucoid lesion as a carcinoma without adequate tissue
- Diagnosis of VC at initial presentation and biopsy is challenging given overall bland cytomorphology and shared features with reactive verrucoid lesions

Verrucous Carcinoma
Biopsy Diagnosis

- “Well-differentiated verrucoid squamous epithelial proliferation, NOS” – complete excision & follow-up
- Recurrence of tumor at a future time may be the most important clue/evidence to diagnosis of VC
Verrucous Carcinoma
Differential Diagnosis

- “Conventional” squamous cell carcinoma
- Reactive verrucoid hyperplasia
- Proliferative verrucous leukoplakia (PVL)
- Papilloma

Proliferative Verrucous Leukoplaia

Diagnosis of PVL requires clinicopathologic correlation

- Suggested criteria to render diagnosis:
  - involvement of more than 2 oral cavity subsites
  - total size of the leukoplakic foci is >3 cm
  - presence of disease for at least 5 years with history of progression and recurrence
### Verrucous Carcinoma

**Treatment and Prognosis**

- Surgery is the treatment of choice
- Radiotherapy used in select settings
- Excellent prognosis:
  - for laryngeal VC: 5-yr survival rates of 86-95%
- Local recurrence but no metastases
  - may cause extensive destruction if left untreated
- Does not metastasize
- Hybrid carcinoma has potential for metastasis and should be treated as conventional SCC

### Viral-Associated Neoplasms of the H&N

- **Human papillomavirus (HPV):**
  - Papilloma (Low-risk)
  - Oropharyngeal carcinoma (High-risk)
- **Epstein-Barr virus (EBV):**
  - Nasopharyngeal carcinoma
  - Hematolymphoid tumors
  - Smooth muscle tumors
- **Merkel cell polyoma virus:**
  - Merkel cell carcinoma
- **Human herpes virus 8:**
  - Kaposi sarcoma
- **Human immunodeficiency virus (HIV):**
  - HNSCC

### Viral-Associated Neoplasms of the Head & Neck

- Oropharyngeal HPV-associated squamous cell carcinoma (WHO 2017 – SCC, HPV-positive):
  - Clinicopathologic features
  - Morphologic variants
  - Ancillary testing & CAP Recommendations
  - Non-squamous malignant neoplasms
- Nasopharyngeal EBV-associated squamous cell carcinoma
- Metastatic cervical carcinoma with unknown primary tumor
### HPV-positive SCC vs HPV-negative SCC

<table>
<thead>
<tr>
<th></th>
<th>HPV-positive SCC</th>
<th>HPV-negative SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>Increasing</td>
<td>Stable to decreasing</td>
</tr>
<tr>
<td><strong>Age/Gender</strong></td>
<td>Younger; M=F</td>
<td>Older; M&gt;F</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Caucasian &gt;&gt;&gt; African American</td>
<td>African American &gt; Caucasian</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>HPV</td>
<td>Smoking, alcohol</td>
</tr>
<tr>
<td><strong>Primary location</strong></td>
<td>Oropharynx (BOT; tonsil)</td>
<td>All UADT mucosal sites</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Nonkeratinizing SCC</td>
<td>Keratinizing SCC</td>
</tr>
<tr>
<td><strong>p16</strong></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>AJCC staging</strong></td>
<td>Lower T, higher N</td>
<td>Higher T, lower N</td>
</tr>
<tr>
<td><strong>Chemotherapy response</strong></td>
<td>Good with low rate of recurrence</td>
<td>Good with high rate recurrence</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Better disease-free &amp; overall survival (worse if smokers)</td>
<td>Worse disease-free and overall survival</td>
</tr>
</tbody>
</table>

### Cervical Neck Lymph Node Stations

- [Diagram of Cervical Neck Lymph Node Stations](image)

### Site Specific Lymph Node Drainage

- [Diagram of Site Specific Lymph Node Drainage](image)
**FNAB Diagnosis**

- Metastatic poorly-differentiated carcinoma favor squamous cell carcinoma
Diagnosis

- Oropharyngeal (Tonsillar) Carcinoma:
  - Poorly-differentiated squamous cell carcinoma
  - Squamous cell carcinoma with basaloid features
  - **Nonkeratinizing carcinoma** - recapitulate tonsillar crypt epithelium so in fact are differentiated and NOT poorly-differentiated cancers and should not be graded as such

Nonkeratinizing Carcinoma

↓

Human Papillomavirus (HPV)

↓

Oropharyngeal Carcinoma

(SCC, HPV-positive WHO 2017)
Invasive Oropharyngeal SCC, Predominantly Nonkeratinizing
Oropharyngeal SCC, HPV-Positive

Metastatic SCC, HPV-positive c/w Oropharyngeal Origin

Metastatic SCC, HPV-positive c/w Oropharyngeal Origin
Hybrid Oropharyngeal SCC

Hybrid Oropharyngeal SCC, HPV-positive

Oropharyngeal SCC, HPV-Positive Morphologic Spectrum

- Nonkeratinizing
- Hybrid
- Papillary SCC (PSCC)
- Basaloid SCC (BSCC)
- Spindle cell SCC (Sarcomatoid carcinoma)
- Adenosquamous (Ciliated cell) carcinoma
- Lymphoepithelial-like
BSCC

Nuclear palisading

Lobular growth, comedonecrosis
Reduplicated basement membrane-like material
BSCC

Perineural invasion

IHC Findings
- IHC:
  - Cytokeratins
  - p63/p40 (diffusely positive)
  - Variable reactivity for S100 protein, NSE
  - Mesenchymal: Vimentin, SMA
  - Negative for neuroendocrine, melanocytic and lymphoid markers
  - p16:
    - Most non-oropharyngeal HPV-negative
    - Most oropharyngeal HPV-positive

Treatment and Prognosis
- Aggressive management:
  - Complete surgical resection
  - Radiotherapy and chemotherapy
- HPV-negative:
  - Dismal prognosis
- Active smokers and those with nodal metastases at presentation have worse prognosis
- Lymphatic and hematogenous spread:
  - Regional lymph nodes (50-70%)
  - Lung, bone, skin and brain
BSCC

- HPV-positive:
  - Better overall prognosis than histologically similar non-HPV associated head and neck BSCC (Am J Surg Pathol 2008;32:1044-50)
- Any tumor appearing to arise in the larynx/hypopharynx but that involves the oropharynx should be tested for HPV (p16)

Adenosquamous (Ciliated Cell) Carcinoma

Adenosquamous (Ciliated Cell) Carcinoma
Adenosquamous (Ciliated Cell) Carcinoma

Ciliated HPV-Associated Carcinoma (aka Ciliated Adenosquamous Carcinoma)


Neuroendocrine Carcinoma (NEC)

Definition

- Heterogeneous group of malignant neoplasms with divergent differentiation along epithelial and neuroendocrine cell lines
NEC of the Head and Neck
2017 WHO Classification

- Well-differentiated NEC (WDNEC) = Carcinoid Tumor
- Moderately-differentiated NEC (MDNEC) = Atypical Carcinoid
- Poorly-differentiated NEC = Small Cell Carcinoma (SmCC)
- Poorly-differentiated NEC = Large Cell Carcinoma (LCNEC)
HPV-Related Small Cell Carcinoma of the Oropharynx

- Bishop & Westra. AJSP 2011;35:1679-1684
- Kraft S, Faquin WC, Krane JF. AJSP 2012;36:321-330
  - 17 cases
  - M > F; 6th-7th decades
  - Tonsil, base of tongue, neck
  - Smoking history
  - Presentation with neck metastases including occult primary
**HPV-Associated Oropharyngeal SmCC**

- Subset of HPV-related oropharyngeal carcinomas with small cell morphology
- Recognition and distinction from HPV-related squamous cell carcinoma important
- Overlapping morphology
- CK5/6 and p63 may represent a key differentiating markers
- Despite presence of HPV, small cell phenotype indicate a greater propensity for aggressive clinical behavior

**PDNEC - LCNEC**

**Clinical Features**

- More common in men than women
- Occur over a wide age range average age of 59 years
- Predilect to the supraglottic larynx >> SNT >>> other
- Most patients are smokers
- May be associated with HPV (Oropharynx, SNT, larynx):
  - Mixed information in the literature relative to prognosis
    - HPV association may not impart more favorable prognosis
Criteria for (Laryngeal) LCNEC

<table>
<thead>
<tr>
<th>Requisite criteria</th>
<th>Other typical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor cells with moderate to abundant cytoplasm</td>
<td>Nuclei with prominent nucleoli</td>
</tr>
<tr>
<td>Features of neuroendocrine differentiation (organoid nesting, trabecular growth, rosettes, and peripheral palisading)</td>
<td>Cellular pleomorphism</td>
</tr>
<tr>
<td>Mitotic activity &gt; 10/10 hpf (2 mm²)</td>
<td>Large areas of necrosis</td>
</tr>
<tr>
<td>Confirmation of neuroendocrine differentiation using immunohistochemical staining</td>
<td></td>
</tr>
</tbody>
</table>
PDNEC - LCNEC
Treatment and Prognosis

- Chemoradiotherapy
- Many patients have disseminated disease at presentation obviating option of laryngectomy and neck dissection
- Commonly present with advanced stage (stages III and IV):
  - may be metastatic to cervical lymph nodes at presentation
  - may be metastatic to distant sites at presentation (e.g., liver)
- 5-year disease specific survival (DSS) of 15-21%

Head and Neck NECs

- Larynx most common site; less common sites include SNT, salivary gland, others
- M > F; generally occurs in the 6th-7th decades of life
- Larynx:
  - Supraglottic larynx overwhelmingly the most common site of occurrence
  - History of cigarette smoking > 60%
  - MDNEC >>> SmCC >> LCNEC >>> WDNEC
- SNT and Salivary Gland (Parotid):
  - SmCC >>> LCNEC >> MDNEC > WDNEC

HPV Testing in HNSCC: Guidelines from CAP
Lewis JS, et al. Arch Pathol Lab med 2018;142:559-597

- Staining with IHC p16:
  - should be used as an initial screening method
  - nuclear & cytoplasmic positivity
  - > 70% cut off
- 14 Guideline statements
  - Strong recommendation
  - Recommendation
  - Expert consensus opinion
  - No recommendation
CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

• #1: Strong recommendation – should perform HR-HPV on all patients with newly diagnosed OPSCC, including all histologic subtypes; on primary tumor or on regional LN metastasis when clinical findings c/w OP origin
• #2: Recommendation – For oropharyngeal tissue specimens (i.e., noncytology), pathologists should perform HR-HPV testing by surrogate marker p16 IHC. Additional HPV-specific testing may be done at the discretion of the pathologist and/or treating clinician, or in the context of a clinical trial

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

• #3: Expert Consensus Opinion – Pathologists should not routinely perform HR-HPV testing on patients with non-SCCs of the oropharynx (neuroendocrine carcinomas; salivary gland carcinomas)
• #4: Recommendation – Pathologists should not routinely perform HR-HPV testing on patients with nonoropharyngeal primary tumors of the H&N
• #5: Recommendation – Pathologists should routinely perform HR-HPV testing on patients with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

• #6: Expert Consensus Opinion – For tissue specimens (i.e., noncytology) from patients presenting with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node, pathologists should perform p16 IHC

NOTE: Additional HR-HPV testing on p16-positive cases should be performed for tumors located outside of level II or III (noncytology testing) in the neck and/or for tumors with keratinizing morphology
CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

• #7: Expert Consensus Opinion – Pathologists should perform HR-HPV testing on head and neck fine needle aspiration (FNA) SCC samples from all patients with known OPSCC not previously tested for HR-HPV, with suspected OPSCC, or with metastatic SCC of unknown primary

NOTE: No recommendation is made for or against any specific testing methodology for HR-HPV testing in FNA samples. If the result of HR-HPV testing on the FNA sample is negative, testing should be performed on tissue if it becomes available. If pathologists use cytology samples for p16 IHC testing, they should validate the criteria (i.e., cutoff) for a positive result.

• #9: Expert Consensus Opinion – Pathologists should not routinely perform low-risk HPV testing on patients with head and neck carcinomas.

• #10: Expert Consensus Opinion - Pathologists should not repeat HPV testing on patients with locally recurrent, regionally recurrent, or persistent tumor if primary tumor HR-HPV status has already been established. If initial HR-HPV status was never assessed or results are unknown, testing is recommended. HPV testing may be performed on a case-by-case basis for diagnostic purposes if there is uncertainty regarding whether the tumor in question is a recurrence or a new primary SCC.

• #11: Expert Consensus Opinion – Pathologists should not routinely perform HR-HPV testing on patients with distant metastases if primary tumor HR-HPV status has been established.

• #12: Expert Consensus Opinion – Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as HPV-positive/p16-positive.

• #13: Expert Consensus Opinion – Pathologists should not provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCCs.
Carcinoma involving Tonsillar Crypt ≠ CIS

**p16 Function**

- p16 functions to activate RB-dependent cell cycle arrest

- p16 functions to activate RB-dependent cell cycle arrest
Distinct oncogenic pathways leading to p16 induction
Nasopharyngeal Carcinoma (NPC)
WHO Classification (2017)

• Keratinizing SCC:
  – well-, moderately, poorly-differentiated (WHO 1)
• Nonkeratinizing SCC:
  – Differentiated type (Transitional Cell or Cylindrical Cell Carcinoma; WHO 2)
  – Undifferentiated type (Lymphoepithelioma; WHO 3)
• Basaloid SCC

<table>
<thead>
<tr>
<th>NPC</th>
<th>Keratinizing</th>
<th>Nonkeratinizing Differentiated</th>
<th>Nonkeratinizing Undifferentiated</th>
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<tbody>
<tr>
<td>Percent</td>
<td>Approximately 25%</td>
<td>Least common &lt; 15%</td>
<td>Most common &gt; 60%</td>
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<td>Sex/Age</td>
<td>M &gt; F; 4th-6th decades</td>
<td>M &gt; F; 4th-6th decades</td>
<td>M &gt; F; 4th-6th decades; may occur in children</td>
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<tr>
<td>EBV</td>
<td>Weak association</td>
<td>Strong association</td>
<td>Strong association</td>
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<tr>
<td>XRT Response</td>
<td>Radioresponsiveness is not good</td>
<td>Radiosensitive</td>
<td>Radiosensitive</td>
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<tr>
<td>5-Yr survival</td>
<td>20-40%</td>
<td>75%</td>
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NPC, nonkeratinizing undifferentiated

NPC, nonkeratinizing undifferentiated

NPC, nonkeratinizing undifferentiated
Metastatic Cervical Carcinoma with an Unknown Primary Tumor (MCCUP)

• Definition:
  - Overt neck mass harboring a cytologically or histologically proven metastatic carcinoma in the absence of signs and symptoms of a primary neoplasm or of a clinically detectable mass:
    • no history of previous malignancy or cancer ablation of any indeterminate lesion
    • no history of definite symptoms related to a specific organ system
    • no clinical or laboratory evidence of a primary neoplasm

Luna MA. Chapter 17. In: Barnes L, ed. Surgical Pathology of the H&N. 2009

<table>
<thead>
<tr>
<th>Primary Tumors</th>
<th>Squamous cell</th>
<th>Adenocarcinoma</th>
<th>Adenoid cystic</th>
<th>Mucoepidermoid</th>
<th>Melanoma</th>
<th>Salivary gland</th>
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<td>36</td>
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<td>Carcinomas</td>
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<tr>
<td>Undifferentiated</td>
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<td>28</td>
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<td>88</td>
<td>210</td>
<td></td>
<td>1</td>
<td>2</td>
<td>506</td>
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Waldeyer Tonsillar Tissues
Branchiogenic Carcinoma Criteria*

- Cervical tumor occurs along line extending from anterior to the tragus along the anterior border of the SCM to the clavicle
- Histology c/w origin from tissue known to be present in branchial vestige
- No primary source for carcinoma on at least 5-year f/u
- Histologic evidence of carcinoma arising in wall of epithelial-lined cyst


Branchial Cleft Cyst

- Benign lateral neck cyst most often of 2nd branchial cleft apparatus
- Bimodal age: 20-40 (75%); <5 yrs (20%):
  - rare (≤5%) in ages >40 years
- Painless cervical swelling typically near angle of mandible along border of SCM
Case History

- 39 year old female presented with an enlarging right sided neck mass at Level IIA (subdigastric lymph node)
- There was no past or current history of malignancy
- The lymph node was excised
Case
Other IHC

- Hematolymphoid markers (CD45; CD20) negative
- Melanoma markers (S100 protein, HMB45, others) negative

Case

Diagnosis

- Metastatic HPV-associated lymphoepithelial-like carcinoma consistent with oropharyngeal origin
- Endoscopic biopsies of UADT sites including oro- and nasopharynx were performed
Lymphoepithelial-like Carcinoma of the Oropharynx: A morphologic variant of HPV-related head and neck carcinoma

Singhi AD, Stelow EB, Mills SE, Westra WH.
Am J Surg Pathol 2010;34:800-805
Squamous Cell Lesions
Summary

• Overview of intraepithelial alterations of the upper aerodigestive tract:
  – focus on keratinizing dysplasia
  – 2 Tier grading system:
    • Low-grade (mild dysplasia)
    • High-grade (moderate & severe dysplasia and CIS)
• Verrucous carcinoma diagnosis

Squamous Cell Lesions
Summary

• Viral carcinogenesis causally associated with HNSCC
• Classification:
  - SCC, HPV-positive (oropharynx)
  - SCC, EBV-positive (nasopharynx)
• Overall better prognosis than non-viral associated HNSCC
• Overlapping morphology between HPV+ and EBV+ cancers:
  - When confronted with MCCUP, both p16 and EBER should be performed
• No correlation to size of primary neoplasm (millimeters) and size of metastasis (centimeters)
  - tiny foci may give rise to large metastases
• Relative to oropharyngeal cancers concept of CIS is not applicable:
  - lesions that morphologically appear to be CIS may metastasize

AJCC Staging 8th Edition

• HPV-mediated (p16+) Oropharyngeal Cancer (Chapter 10):
  - Descriptor “poorly-differentiated” at odds with known improved prognosis so use should be avoided
  - Use of the designation “oropharyngeal SCC, nonkeratinizing type” is recommended
  - Histologic grading is not relevant
  - Presence of keratinization in a p16+/HR HPV+ carcinoma does not exclude using this staging system
  - Cervical lymph node metastases (to level II/III) from unknown primary tumor (pT0) that is p16+ and histology is consistent with HPV-mediated carcinogenesis are staged according to the guidelines in this chapter
  - Diagnosis of malignant transformation of branchial cleft cyst “should be rejected”
Squamous Cell Lesions

Summary

- New WHO Classification of H&N PDNEC includes small cell and large cell types
- PDNEC may also metastasize without a known primary particularly of oropharyngeal origin:
  - May be HPV+ (not associated with more favorable prognosis)

Questions?

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