Update on New ENT WHO

Nasal Cavity and Paranasal Sinuses
2005 edition: 76 diagnoses
2017 edition: 39 diagnoses

Inclusion Criteria
1. The tumor occurs exclusively at this site;
2. The tumor also occurs at other head and neck sites but has a predilection for the sinonasal tract; or
3. The tumor is important for differential diagnostic reasons

Specifically, salivary gland neoplasms, bone and cartilage tumors, and hematolymphoid tumors were only recorded once in the book rather than repeated in each anatomic site

Non-keratinizing Squamous Cell Carcinoma

Non-keratinizing squamous cell carcinoma (NKSCC) is a squamous cell carcinoma (SCC) characterized by a distinctive ribbon-like growth pattern with absent to limited maturation

- Synonyms: Schneiderian carcinoma; transitional cell carcinoma; cylindrical cell carcinoma
- Epidemiology: ~20% of sinonasal SCC
- Age: 6th — 7th decades  Sex: M > F
- Pathology: smooth stromal interface with a pushing border; immature appearance with minimal or no keratinization; high N:C ratio; may have peripheral palisading; numerous mitoses; necrosis
Non-keratinizing Squamous Cell Carcinoma

- Sinonasal papilloma with malignant transformation
- Sinonasal undifferentiated carcinoma
- Neuroendocrine carcinoma
- Solid variant of adenoid cystic carcinoma
- SMARCB1 (INI-1) deficient carcinoma
- Rhabdoid and poorly differentiated features
- NUT carcinoma
- "Abrupt" keratinization

HPV-related carcinoma with adenoid cystic-like features

- A distinctive human papillomavirus (HPV)-related carcinoma of the sinonasal tract with histologic and immunophenotypic features of both surface-derived and salivary gland carcinoma, the latter showing the appearance of a high grade adenoid cystic carcinoma (ACC)
- Sex: Female >> Male (7:2)
- Age: 40 — 75 years
- Highly cellular proliferation
- Solid nests with frequently encountered cribriform structures separated by thin collagenized fibrous bands
- Basaloid cells align around cylindromatous microcystic spaces
- Hyperchromatic and slightly angulated nuclei with a high nuclear-to-cytoplasmic ratio
- True ductal cells are present, often with peripheral myoepithelial cells

Sinonasal Undifferentiated Carcinoma

Undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable

- Sinonasal undifferentiated carcinoma (SNUC) is rare
- 3-5% of sinonasal carcinomas
- Age: 50 — 60 years
- Sex: 70% male
- Pathology: sheets, lobules, and trabeculae; moderately large, round nuclei, variable amount of cytoplasm, and well-defined cell borders; limited pleomorphism; nuclei vary from hyperchromatic to vesicular, with open chromatin with prominent nucleoli; apoptosis, mitoses, and necrosis are frequent
- By definition: no squamous and no glandular differentiation
- HPV-HR ISH
- But, carcinoma in situ and surface dysplasia may be seen
L.D.R. Thompson

Update on New ENT WHO

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**Sinonasal Undifferentiated Carcinoma**

**Differential Diagnosis**

- Lymphoma, nonkeratinizing squamous cell carcinoma (SCC), basaloid SCC, and neuroendocrine carcinoma
  - SCC has areas of histologic squamous differentiation, consistently reactive with cytokeratin 5/6, p63, and p40
  - Neuroendocrine carcinomas have speckled salt-and-pepper nuclear chromatin, with strong reactivity with neuroendocrine markers
  - Poorly differentiated carcinomas with rhabdoid features may show a loss of SMARCB1 (INI-1) protein by immunohistochemistry, suggesting a different tumor category
  - NUT carcinoma has evidence of squamous differentiation, and is consistently and diffusely positive for p63 and p40, with strong NUT protein by immunohistochemistry
**SMARCB1 (INI1) deficient carcinoma**

Inactivation of SMARCB1 (INI-1) defines a diverse family of neoplasms

- **Age:** Wide age range (28 — 78 years, mean: 54 years)
- **Sex:** Slight female predominance
- **Pathology:**
  - Undifferentiated basaloid nests
  - High mitotic rates, frequent necrosis
  - Relatively monotonous basaloid cells
  - Rhabdoid or plasmacytoid features
  - Round to oval nuclei
  - No keratinization
- **Biallelic inactivation of SMARCB1 (INI1)**
  - Loss of nuclear SMARCB1 immunohistochemistry
  - Clinically aggressive carcinomas that are frequently associated with local recurrence, regional and distant metastases, and patient death

**NUT Carcinoma**

NUT carcinoma is a poorly differentiated carcinoma, often with evidence of abrupt squamous differentiation, defined by the presence of NUT (nuclear protein in testis, NUTM1) gene rearrangement

- Rare in the upper aerodigestive tract
- **Age:** median: 22 years
- **Sex:** slight female predominance
  - F > M (55:45)
- **The etiology is unknown**
  - No association with human papillomavirus, Epstein Barr virus, other viral infection, smoking, or other environmental factors
  - If head & neck involvement, sinonasal tract is common (65%)
  - Generally, but not always midline
  - Non-specific symptoms; rapidly growing mass
  - Lymph node metastases seen in up to 50% of sinonasal tract cases

**Pathology**

- Poorly differentiated carcinoma arranged in sheets and nests
- Intermediate, round to oval nuclei in monotonously similar tumor cells
- Chromatin: vesicular with distinct nucleoli
- Cytoplasm: scant to moderate; may be clear
- Brisk mitoses
- Tumor necrosis often present
- "Abrupt" foci of keratinization, keratin pearl formation or squamous differentiation
- Intratumoral acute inflammation may be seen
- Glandular and mesenchymal differentiation is infrequent
Unequivocal diagnosis when diffuse (>50%) nuclear staining with the NUT monoclonal antibody

**Positive:** p63, p40 and cytokeratins; CD34 (~55%), neuroendocrine markers, p16 overexpression, TTF-1

**Variable:**

Gene expression of NUTM1 on chromosome 15q14 is fused with BRD4 (70%), BRD3 (6%), or NSD3, creating chimeric genes that encode NUT fusion proteins. NUTM1 is fused to an unknown partner gene (NUT variant) in some cases.

Fluorescent in situ hybridization (FISH), reverse-transcriptase PCR, conventional cytogenetics, and targeted next-generation sequencing may be used to confirm diagnosis.
NUT Carcinoma

- Differential diagnosis:
  - Poorly differentiated squamous cell carcinoma (including SMARCB1 [INI-1] deficient carcinoma), Ewing sarcoma, sinonasal undifferentiated carcinoma, leukemia, germ cell tumors, olfactory neuroblastoma, rhabdomyosarcoma
  - Prognosis is poor: median survival of 9.8 mo.
  - Some evidence suggests that NUT-variant patients may have a longer survival than BRD patients

Neuroendocrine Carcinoma

Sinonasal neuroendocrine carcinoma (SNEC) is a high-grade carcinoma with morphologic and immunohistochemical features of neuroendocrine differentiation, that include small cell carcinoma (SmCC) and large cell neuroendocrine carcinoma (LCNEC)

- Rare: ~3% of sinonasal tumors
- Age: mid to older aged men
- Mean: 40 — 55 years for SmCC
- Mean: 49 — 65 years for LCNEC
- Site: Ethmoid > nasal cavity > maxillary & sphenoid
- Rare association with transcriptionally-active high-risk HPV, previous irradiation
- No significant association with smoking
- Non-specific symptoms, rarely paraneoplastic syndromes
- Advanced local disease with regional or distant metastases at presentation

Neuroendocrine Carcinoma

- SmCC is histologically identical to lung
  - Small cells, nuclear molding, cannibalism, necrosis, limited nucleoli, high mitoses
  - Highly infiltrative with frequent perineural and lymphovascular invasion
- LCNEC contains large cells that show light microscopic neuroendocrine features

Small cell

Large cell
Neuroendocrine Carcinoma

- **Positive:**
  - Strongly positive for cytokeratins (CAM5.2, AE1/AE3) and EMA, often perinuclear or dot-like pattern
  - Neuroendocrine markers (synaptophysin better than chromogranin, NSE or CD56)
  - S100 protein, when positive is diffuse rather than sustentacular
  - p16

- **Variable:**
  - p63, calretinin

- **Negative:**
  - CK5/6, EBER, CK20

Non-intestinal-type Adenocarcinoma

*Adenocarcinoma of the sinonasal tract that cannot be best classified as salivary gland neoplasia and do not have an intestinal phenotype. While the tumors are morphologically heterogeneous, this category may include some specific entities that are morphologically unique (e.g., renal cell-like carcinoma)*
High grade

Non-intestinal-Type Adenocarcinoma
Renal cell-like Adenocarcinoma

- Composed predominately of clear cells, reminiscent of renal cell carcinoma
- Tumors are composed of monomorphous cuboidal to columnar glycogen-rich clear cells that lack mucin production
- The cytoplasm may be “clear” or slightly eosinophilic
- Absent: perineural invasion, lymphovascular invasion, necrosis, and marked pleomorphism
- **Positive:** CAIX, CD10
- **Negative:** PAX8, RCC

Sinonasal papillomas

- No eponyms
- Conrad Victor Schneider
- German anatomist at University of Wittenberg
- Published in 1660 about nasal mucous membrane as the source of nasal secretions (rather than pituitary in the brain)
Sinonasal papillomas

- Sinonasal papilloma inverted type
  - A papilloma derived from sinonasal tract surface mucosa that usually shows inverted growth and has multilayered epithelium with mucocytes and transmigrating neutrophils

- Sinonasal papilloma oncocytic type
  - A papilloma derived from the sinonasal epithelium composed of both exophytic fronds and endophytic invaginations lined by multiple layers of columnar cells with oncocytic features. Intraepithelial microcysts containing mucin and neutrophils are characteristic

- Sinonasal papilloma exophytic type
  - A papilloma derived from the sinonasal mucosa composed of papillary fronds with delicate fibrovascular cores covered by multilayered epithelium

Respiratory Epithelial Adenomatoid Hamartoma

Respiratory epithelial adenomatoid hamartoma (REAH) is a benign acquired overgrowth of indigenous glands of the sinonasal tract arising from the surface epithelium

- Age: Median: 6th decade
- Sex: Male predominance

Pathology:
- Widely-spaced, small to medium glands separated by stromal tissue
- The glands arise in direct continuity with the surface epithelium, invaginated downward
- Glands composed of multilayered ciliated respiratory epithelium, admixed mucin secreting (goblet) cells
- Glands surrounded by a thickened, eosinophilic basement membrane is characteristic

Seromucinous Hamartoma

Seromucinous hamartoma (SH) is benign overgrowth of indigenous seromucinous glands of the nasal cavity and paranasal sinuses

- Extremely rare
- Age: Mean: 56 years
- Sex: Male > Female (3:2)
- Site: Posterior nasal septum or nasopharynx
Seromucinous Hamartoma

- Polypoid mass covered by respiratory epithelium
- Small to large glands and ducts, lined by a single layer of cuboidal or flattened epithelial cells
  - Eosinophilic secretion can be seen in the lumen
- Intermingled with the pre-existing seromucinous acini similar to respiratory epithelial adenomatoid hamartoma (REAH): probably a spectrum of lesions
- Tubular glands may be encircled by thick basement membrane
- Bland oval to round nuclei and amphophilic to eosinophilic cytoplasm
  - Goblet or clear cells may be seen
- Mitoses are absent

**Immunohistochemistry:**
- Positive: Keratins, EMA and S100 protein
- Negative: p63, CK5/6 (myoepithelial [basal] markers)

Chondromesenchymal Hamartoma

**Benign, locally destructive, tumor-like growth containing mixed mesenchymal elements**

- **Age:** Infants   **Sex:** Male > Female
- **Pathology:**
  - Lobular proliferation of mature and immature hyaline cartilage with variably cellular fibrous stroma;
  - Bony trabecular may be seen
  - May be seen with pleuropulmonary blastoma associated *DICER1* familial tumor susceptibility syndrome
Biphenotypic sinonasal sarcoma (BSNS) is a low grade spindle cell sarcoma with distinctive histologic, immunohistochemical, and molecular features, most frequently characterized by a recurrent PAX3-MAML3 gene fusion.

- **Synonym:** Low grade sinonasal sarcoma with neural and myogenic features
- **Sex:** Female > Male (2:1)
- **Age:** Mean, 52 years (range: 24 — 85 years)
- **Site:** Multiple sites, especially superior aspect of the nasal cavity and ethmoid sinus, with extension to orbit or cribriform plate
- **Symptoms:** Nonspecific, but usually a mass

Pathology:

- Cellular submucosal spindle cell proliferation
- Unencapsulated and infiltrative, including into bone
- Elongated spindle cells arranged in medium to long intersecting fascicles, sometimes "herringbone" appearance
- Scant, delicate collagen matrix
- Nuclei are uniform and slender
- Few mitoses
- Streaking proliferation of the epithelium, with invaginations intimately admixed with neoplastic cells
  - Squamous or oncocytic metaplasia resembles sinonasal papilloma
- May show a prominent hemangiopericytoma-like vascular pattern
- Focal rhabdomyoblastic differentiation (11%) is associated with an alternate fusion partner
- **Positive:** S100 protein; SMA and/or MSA
  - Staining may be focal, patchy, or diffuse
- **Variable:** CD34, desmin, myoD1, myogenin, EMA, keratin

S100 protein staining
Chromosomal translocation t(2;4)(q35;q31.1)
- An in-frame fusion of exon 7 of transcription factor PAX3 to exon 2 of MAML3, a co-activator of the Notch signaling pathway
- PAX3-MAML3 is found in most tumors (highly expressed)
- A subset harbor the alternate fusion genes, including PAX3-FOXO1 and PAX3-NCOA1 (similar to alveolar rhabdomyosarcoma)
- Slow progression with local destruction
- Local recurrences are common (50%)
  - up to 9 years after initial treatment
- No metastatic disease or death from disease reported

Sinonasal Glomangiopericytoma
- A sinonasal tumor demonstrating perivascular myoid phenotype
- Rare tumors (<0.5% of SNT neoplasms)
- Age: Peak 7th decade Sex: Slight F > M
- Positive: Actins (SMA>MSA), nuclear β-catenin
- Negative: CD34, CD31, CD117, STAT6, EMA, keratin, S100 protein, desmin
- Genetics:
  - Somatic, single nucleotide substitution heterozygous mutations in CTNNB1 gene encoding β-catenin, specifically in GSK3β region (encoded by exon 3)
  - Activation of β-catenin with cyclin D1 over expression are important pathogenetic events

Solitary Fibrous Tumor
- Solitary fibrous tumor is a fusion gene-associated tumor of fibroblastic phenotype with a branching vasculature
- Solitary fibrous tumors (SFT) are rare
- Adults without gender predilection
- Pathology:
  - Submucosal, pseudoencapsulated and variably cellular, with bland spindle-shaped cells
  - Haphazard architecture
  - Stellate to staghorn-like vessels
  - Variable collagenous background
- Positive: STAT6 (nuclear), CD34, bcl-2
- Genetics: NAB2-STAT6 fusion seems specific

Biphenotypic Sinonasal Sarcoma
- Chromosomal translocation t(2;4)(q35;q31.1)
  - An in-frame fusion of exon 7 of transcription factor PAX3 to exon 2 of MAML3, a co-activator of the Notch signaling pathway
  - PAX3-MAML3 is found in most tumors (highly expressed)
  - A subset harbor the alternate fusion genes, including PAX3-FOXO1 and PAX3-NCOA1 (similar to alveolar rhabdomyosarcoma)
  - Slow progression with local destruction
  - Local recurrences are common (50%)
    - up to 9 years after initial treatment
  - No metastatic disease or death from disease reported
L.D.R. Thompson

Update on New ENT WHO

Larynx
2005 edition: 44 diagnoses
2017 edition: 22 diagnoses
Dysplasia

- A spectrum of architectural and cytological epithelial changes caused by an accumulation of genetic changes that is associated with an increased likelihood of progression to squamous cell carcinoma
- Uncommon
- Age: Adults
- Sex: Male > Female (4.6:1)
- Etiologically related to alcohol and tobacco smoking (synergistic), gastroesophageal reflux with HPV a very minor role

Dysplasia

- Most commonly along one vocal cord, although bilateral disease may occur
  - Commissures are uncommonly involved
- Voice changes, hoarseness, sore throat, chronic cough
- Leukoplakia, erythroplakia or combination
- Diffuse, flat, exophytic to papillary

Normal
L.D.R. Thompson

Update on New ENT WHO

Basal zone hyperplasia

Low-grade dysplasia (including previous category of mild dysplasia):
Low malignant potential, a spectrum of morphological changes ranging from squamous hyperplasia to an augmentation of basal and parabasal cells occupying as much as the lower half of the epithelium, while the upper parabasal epidermis is normal.

Architectural criteria:
- Stratification is preserved transition of basal cells or augmented basolabial cell layer with perpendicular orientation to the basement membrane in prickle cells horizontally oriented in the upper part.
- The nuclei are hyperchromatic.
- Basal parabasal layer: spectrum of changes, from 2-0 unaltered layers to augmentation of basal and parabasal cells in the lower half of the epithelium.

Cytological criteria:
- Parabasal cells: slightly increased cytoplasm compared to basal cells, enlarged nuclei, uniformly distributed chromatin, no intercellular bridges.
- Rare regular mitoses in or near basal layer.
- Few dyskeratotic cells present.

LG dysplasia

LG dysplasia
L.D.R. Thompson

Update on New ENT WHO

LG dysplasia

HG dysplasia (moderate)
Update on New ENT WHO

HG dysplasia (moderate)

HG dysplasia

HG dysplasia (severe)

HG dysplasia (severe)

HG dysplasia (severe)
Treatment and Outcome

- Biopsy, stripping, laser, cryotherapy and radiation variably employed
- Malignant progression:
  - Low grade: 2%
  - High grade: 12.5-40% (CIS is 40%)
- Anatomic site, multifocality, age, comorbidities (including alcohol and tobacco) contribute to progression

Oropharyngeal Carcinoma

Definition

Oropharyngeal squamous cell carcinoma (OPSCC) is a malignant epithelial neoplasm involving the oropharynx which includes:

- Soft palate
- Tonsils and adenoids (Waldeyer ring)
- Uvula
- Base of tongue
- Oropharyngeal wall
Etiology/Pathogenesis

- Environmental Exposure
  - Marijuana use is greater in HPV+ OPSCC
  - Tobacco smoking and alcohol use greater in HPV- OPSCC, but still a major factor in HPV+ OPSCC
- Infectious Agents
  - High-risk HPV associated with >80% of cases OPSCC
    - HPV 16 is the predominant type
    - Other HPV high-risk types are reported

Epidemiology

- OPSCC increased 1-2% annually in USA males in past 20 years
  - In USA, 225% increase in HPV+ OPSCC between 1984-2004
  - ~13,000 new cases/year in US

Epidemiology

- It is a sexually transmitted disease:
  - Higher than average sex history
  - Oral sex, multiple partners
- Sex: Male (~95%)
- Age: 50-60's
- Race: Caucasian
- History of smoking
  - Mostly light or former

Presentation

- Site:
  - Anterior tonsillar pillar and fossa most common
- Tongue base
- Early lesions generally asymptomatic
- Tonsillar asymmetry
- Dysphagia
- Otalgia
- Trismus
- Enlarging cervical lymph node
  - Often presenting symptom
- > 70% of patients present with stage III or IV disease
Imaging Findings

- Computed tomography (CT) &/or magnetic resonance imaging (MR) for preoperative tumor staging and planning
- Chest CT or plain film to rule out lung metastases
- Positron emission tomography (PET) useful particularly when dealing with unknown primary or in evaluating distant metastases
  - Distant metastases uncommon in oral cavity cancer at presentation
Squamous Cell Carcinoma

- There are 3 major carcinoma types in the upper aerodigestive tract that do not progress through dysplastic precursors
  - Basaloid squamous cell carcinoma
  - Nonkeratinizing squamous carcinoma
  - Lymphoepithelial carcinoma

Microscopic Features

- **HPV positive types**
  - Oropharyngeal SCC, non-keratinizing
  - Oropharyngeal SCC, keratinizing

- **HPV negative types**
  - Oropharyngeal SCC, non-keratinizing
  - Oropharyngeal SCC, keratinizing

HPV Detection Methods

- Show biologically or transcriptionally-active HPV
  - Polymerase chain reaction
    - RT-PCR for high risk E6/E7 mRNA
  - In situ hybridization
    - Multiplexed (High risk vs. low risk)
    - Type specific probes
  - Other methods
    - Hybrid capture (cytology samples)
    - Other technologies
  - p16 immunohistochemistry

Onogenesis of HPV

HPV protein E7 degrades the retinoblastoma protein leading to aberrant overexpression of p16

Courtesy Dr. J. L. Hunt
L.D.R. Thompson

**Update on New ENT WHO**

<table>
<thead>
<tr>
<th>Study</th>
<th>% of p16 Positive Patients</th>
<th>HPV DNA PCR</th>
<th>HPV DNA ISH</th>
<th>HPV RNA RTPCR</th>
<th>HPV ISH &amp; DNA PCR</th>
<th>HPV RNA RTPCR</th>
<th>HPV ISH &amp; DNA PCR</th>
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<tbody>
<tr>
<td>Dahlstrand, Anticancer Res 2005</td>
<td>16</td>
<td>15 (93%)</td>
<td>NP</td>
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<td>Weinberger, JCO 2006</td>
<td>18</td>
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<td>Reimer, Int J Cancer 2007</td>
<td>29</td>
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<td>Aug, JCO 2008</td>
<td>206</td>
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<td>192 (93%)</td>
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<td>Leco, JCO 2008</td>
<td>187</td>
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<td>Ups, JCO 2001</td>
<td>148</td>
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<td>119/145 (75%)</td>
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<td>NP</td>
<td>147/148 (97.9%)</td>
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<td>Nohales, Int J Cancer 2001</td>
<td>11</td>
<td>NP</td>
<td>6/10 (60%)</td>
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<td>10 (90.9%)</td>
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<td>Sherrying, JCO 2005</td>
<td>90</td>
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<td>75 (83.3%)</td>
<td>68 (97.3%)</td>
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<td>Whitney, JCO 2001</td>
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<td>24 (96.0%)</td>
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<td>Totals</td>
<td>730</td>
<td>57/63 (90%)</td>
<td>555/658 (82%)</td>
<td>249/277 (89.8%)</td>
<td>10/11 (100%)</td>
<td>147/148 (99%)</td>
<td>128</td>
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</table>

**HPV Detection methods**

- Approximately 5% of p16 positive were HPV-
  - However, p16 may be over-expressed by another mechanism
- Approximately 2% of p16 negative cases were HPV+
- p16 is a sensitive marker for transcriptionally active HPV
  - Clone E6H4 (MTM Laboratories) gives best results
- Must be >70% nuclear & cytoplasmic positive

**WHO Classification Book-2017**

**5. Tumours of the oropharynx (base of tongue, tonsils, adenoids)**

**5.1. Introduction**

In recognition of the distinctive anatomic, histologic, and clinical features of this group of tumours, a separate chapter on this topic is placed in this book.

**5.29. Squamous cell carcinoma, HPV-positive**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HPV-positive oropharyngeal SCC</th>
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<tbody>
<tr>
<td>Moderately differentiated SC</td>
<td>50-60 years</td>
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<tr>
<td>HPV associated risk factors</td>
<td>Squamous metaplasia</td>
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<tr>
<td>Lymph node metastasis</td>
<td>Carcinomatous</td>
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</table>

**Microscopic Features**

**HPV-positive OPSCC**

- **OPSCC, Nonkeratinizing type (75% of cases)**
  - Tumor often seen arising from epithelium of tonsillar crypts rather than overlying epithelium
  - Basaloid oval to spindle-shaped cells with hyperchromatic nuclei and minimal cytoplasm forming trabeculae, sheets, or nests with sharply defined borders
  - Comedo-necrosis frequently present
  - Brisk mitotic rate and numerous scattered apoptotic cells
  - Permeated by lymphocytes
  - Squamous maturation and focal areas of keratinization can be seen but should comprise <10%
Microscopic Features
HPV-positive OPSCC

• OPSCC, Lymphoepithelial-like
  ◆ Similar in histology to EBV-related nasopharyngeal carcinoma
  ◆ Syncytial-appearing large tumor cells with indistinct cell borders and vesicular nuclei intermingled with lymphocytes and plasma cells

• OPSCC, Papillary
  ◆ Exceedingly uncommon morphologic variant of SCC that can occur in oropharynx
  ◆ Finger-like projections of cytologically malignant epithelial cells with fibrovascular cores
Microscopic Features
HPV-negative OPSCC

- OPSCC, Keratinizing
  - Exhibits features of conventional-type SCC, including nests of epithelial cells with abundant eosinophilic cytoplasm and well-defined cell borders
  - Frank keratinization present
  - Basaloid morphology not seen
Tumor Type: p16 and HPV reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Nonkeratinizing (54%)</th>
<th>Nonkeratinizing with maturation (21%)</th>
<th>Keratinizing (25%)</th>
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<tbody>
<tr>
<td><strong>p16</strong></td>
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<td>Positive</td>
<td>98%</td>
<td>84%</td>
<td>19%</td>
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<tr>
<td>Negative</td>
<td>2%</td>
<td>16%</td>
<td>81%</td>
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HPV

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<tr>
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<th>Positive</th>
<th>Negative</th>
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<tr>
<td><strong>HPV</strong></td>
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<tr>
<td>Positive</td>
<td>88%</td>
<td>74%</td>
</tr>
<tr>
<td>Negative</td>
<td>12%</td>
<td>26%</td>
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</table>

Immunohistochemistry

- **p16** strongly positive in HPV-associated OPSCC
  - >70% both nuclear & cytoplasmic staining of tumor cells
  - Normal epithelium is negative or shows minimal patchy staining
  - p16 considered reliable surrogate marker for high risk
- **BE AWARE:** p16+ alone DOES NOT equal oropharyngeal carcinoma!
  - There are many lesions that can be p16 positive

Treatment & Prognosis

- Approaches depend on clinical stage
  - Tonsillectomy for small T1 tumors confined to tonsil
  - Radiation therapy, specifically intensity-modulated radiation therapy (IMRT) (including brachytherapy)
  - Concurrent radiotherapy with multiagent chemotherapy
  - Targeted agents such as cetuximab
- **Prognosis**
  - HPV-positive OPSCC associated with improved survival outcomes
  - Tumor size and presence of metastases influence prognosis
L.D.R. Thompson

**Prognosis**

- **Radiation:**
  - HPV+
  - HPV-
  - 5 year survival: 62% vs. 26%

- **Tobacco use:** Decreased survival

- **Nodal status:** Decreased survival

- Patients can be stratified into de-escalation therapies

- E6 and E7 oncoprotein can be targeted, restoring p53 and retinoblastoma tumor suppressor pathways (degraded by E6/E7)

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**Pertinent Issues**

- Do not diagnose OPSCC as in-situ
- Do not give tumor grades for OPSCC
- Report:
  - Oropharyngeal squamous cell carcinoma
  - Non-keratinizing; with maturation; or keratinizing types (for clarity)
  - Report p16 as part of the original report

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**Survival: Radiation vs. Chemotherapy**

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**Radiotherapy and Oncology, Volume 103, Issue 1, 2012, 49 - 56**

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**Base of Tongue**
L.D.R. Thompson

HPV-associated Neuroendocrine Oropharyngeal carcinoma

Synaptophysin

Branchial Cleft Cyst with p16

p16

p16