Keratinizing Dysplasia and Variants of Head & Neck Squamous Cell Carcinoma

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Moffitt Cancer Center
Tampa, FL

Head & Neck Squamous Cell Lesions Outline

• Keratinizing Dysplasia
• Squamous cell carcinoma:
  – Microinvasive and Invasive
• Select Variants
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>Drop-shaped rete ridges</td>
<td>Abnormal variation in cell size</td>
</tr>
<tr>
<td>Increased number of nucleoli</td>
<td>Increased number and size of nucleoli</td>
</tr>
<tr>
<td>Abnormally superficial nucleoli</td>
<td>Increased N:C ratio</td>
</tr>
<tr>
<td>Dyskeratosis in single cells</td>
<td>Atypical nucleoli</td>
</tr>
<tr>
<td>Keratin pearls in rete ridges</td>
<td>Hyperchromasia</td>
</tr>
<tr>
<td>Loss of epithelial cell cohesion</td>
<td>Glandular dysplasia</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

![Dyskeratosis Image](image.png)
Dyskeratosis

Paradoxical Maturation

Keratosis without Dysplasia
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
Carcinoma In Situ

Upper Aerodigestive Tract
Epithelial Dysplasia

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

Keratinizing Mild Dysplasia
Moderate? Severe? CIS?

“Drop Off” Carcinoma

Carcinoma
“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>McGavran (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>
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<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>Silamukhi (1989)</td>
<td>604</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Hojset (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>Total</td>
<td>1106</td>
<td>36 (3.3%)</td>
<td>5.25 (average)</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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<tr>
<td>McGavran (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>
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<tr>
<td>Henry (1979)</td>
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<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>
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<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>Silamukhi (1989)</td>
<td>317</td>
<td>44</td>
<td>13.9</td>
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<tr>
<td>Hojset (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>Total</td>
<td>773</td>
<td>118 (15.3%)</td>
<td>18.4 (average)</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

Binary Grading – Laryngeal Dysplasia

2017 WHO Blue Book

<table>
<thead>
<tr>
<th>Level of abnormality (WHO 2015)</th>
<th>WHO 2015 (146)</th>
<th>SIN classification (88)</th>
<th>Ljubljana classification (76)</th>
<th>Amended Ljubljana classification (79)</th>
<th>WHO 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous hyperplasia</td>
<td>Squamous hyperplasia</td>
<td>Squamous hyperplasia</td>
<td>Low-grade SIL, Low-grade dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>SIN 1</td>
<td>Basaloid (89)</td>
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<td></td>
<td></td>
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<tr>
<td>1/3 to 1/2</td>
<td>Moderate dysplasia</td>
<td>SIN 1 or SIN 2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Upper 1/2 to 3/4</td>
<td>Moderate dysplasia</td>
<td>SIN 1 or SIN 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately hyperplasia</td>
<td>SIN 2</td>
<td>Low-grade hyperplasia</td>
<td>High-grade SIL, High-grade dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>Carcinoma in situ</td>
<td>Carcinoma in situ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In a three-tier system is used, carcinoma 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>Low dysplasia</td>
<td>1</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>2</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>3 (High grade)</td>
</tr>
</tbody>
</table>

The cutoff point between low-grade and high-grade dysplasia, as suggested by Kajani-O et al (1992), is four architectural and five cytological changes (see Table 4.01), irrespective of the level within the epithelium. According to Nairnelli P et al (1972), a cut-off point of four architectural and four cytological changes may improve reproducibility.

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

Oral Dysplasia and High Risk Human Papillomavirus  
(HR-HPV)

- Presence of HR-HPV infection has been convincingly demonstrated in some oral keratinizing dysplasias*:
  - Majority clinically oral leukoplakias
  - Most adult men; Tongue > FOM >> other sites
  - Karyorrhexis and apoptosis with brightly eosinophilic apoptotic cells throughout the thickness of the epithelium, surrounded by keratinocytes exhibiting conventional dysplastic changes
  - Positive for p16 and high-risk HPV subtypes
Oral Dysplasia and HR-HPV

- HR-HPV associated with a subset of severe epithelial dysplasia or carcinoma in situ characterized by:
  - Most adult men; ventral tongue or FOM
  - Diffuse loss of squamous differentiation & high proliferation index throughout basal and suprabasal epithelial layers
- Identified by p16 IHC staining followed by ISH with probes for HPV DNA


HR-HPV FOM Dysplasia

HR-HPV FOM Dysplasia
HR-HPV FOM Dysplasia

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
Squamous Cell Carcinoma

“Early” or Microinvasive Carcinoma

- Neoplastic cells penetrated basement membrane with invasion into submucosa
- Develops as a continuum from keratinizing high-grade dysplasia
- Classically defined CIS is not a prerequisite to the development of invasive carcinoma

Squamous Cell Carcinoma

Microinvasive Carcinoma (MIC)

- No uniformity in defining MIC:
  - small number of cells below BM
  - invasion through the BM
  - invasion through the BM limited to 1-2mm of BM without angioinvasion
  - invasion no more than 0.5mm from epithelial BM with no angioinvasion

Invasive SCC

Diagnostic Features

- Irregular shaped nests within the submucosa with associated dysplastic changes:
  - Hyperchromasia; ↑ N:C; dyskeratosis; ↑ mitotic activity including atypical mitoses
- Desmoplasia
- Invasion:
  - Lymph-vascular invasion; perineural invasion; invasion of soft tissues and/or bone
- Keratin granuloma formation
Invasive SCC

(Micro)Invasive SCC?
HNSCC
Factors Associated with Prognosis

- Adequacy of resection (surgical margins)
- Pattern of invasion: cohesive v dyscohesive
- Tumor size, thickness, location
- LVI, neurotropism and soft tissue invasion
- Regional metastasis - Extranodal Extension
- Distant metastasis
- Angiogenesis; Host immune response
- Second malignancy
Lesions that may be mistaken for squamous cell carcinoma

Necrotizing Sialometaplasia

Necrotizing Sialometaplasia
Necrotizing Sialometaplasia

Necrotizing Sialometaplasia

Necrotizing Sialometaplasia
Post-Irradiation-Associated Changes

- Radiation associated injury to UADT, including the larynx (and pharynx) fairly common owing to use of radiation treatment as primary therapy for mucosal-based carcinomas, especially SCC
- Radiation injury to mucosal sites includes alterations:
  - surface epithelium
  - minor salivary glands
  - stromal cells (fibroblasts, skeletal muscle and endothelial cells)
Post-Irradiation-Associated Changes

• Acute:
  – days to weeks (usually 6 weeks) following treatment
• Chronic:
  – 6-7 weeks following therapy to years later
• Biopsies taken primarily exclude possibility of (recurrent) carcinoma:
  – not uncommonly requested as an intraoperative consultation (i.e., frozen section)

Post-Irradiation-Associated Changes

Histopathology

• Acute changes (biopsies seldom obtained):
  – degeneration and focal necrosis of basal zone epithelium
  – submucosal edema with dilation of capillaries and associated swelling of endothelial cells
  – glandular and acini distension containing mucus
  – superficial erosions with pseudomembranes (3-4 weeks post-radiation)
  – approximately 1 month following initiation of therapy squamous epithelium usually shows complete restoration although thinner than normal

• Chronic changes:
  – Squamous epithelium:
    • thinner than normal; ulceration; epithelial atypia
  – Minor salivary glands:
    • atrophy
    • squamous metaplasia (sialometaplasia):
      – may include marked cytologic atypia suggesting a possible diagnosis of squamous cell carcinoma
      – in contrast to invasive squamous cell carcinoma typically results in effacement of lobular architecture of minor salivary glands, retention of lobulated outline of minor salivary glands supporting diagnosis of sialometaplasia
Post-Irradiation-Associated Changes
Histopathology

- Chronic changes:
  - Connective tissues:
    - submucosal fibrosis
    - vascular alterations characterized by telangiectatic capillaries often with prominent (plump) endothelial cells, myointimal proliferation, foamy histiocytes within the intima and thrombosis
    - bizarre striated muscle degeneration

- Chronic changes:
  - Connective tissues:
    - atypical (bizarre) fibroblasts:
      - appear as individual cells with “smudged” appearing nuclei
      - absence of cohesive cellular grouping as may be seen in invasive carcinoma
      - IHC staining for epithelial markers (e.g., cytokeratins, p63, others) may be required to differentiate squamous cell carcinoma (positive staining) from radiation-induced atypical fibroblasts (negative staining)
Variants of Squamous Cell Carcinoma of the Upper Aerodigestive Tract
Squamous Cell Carcinoma Variants

- Verrucous Carcinoma
- Spindle Cell Squamous Carcinoma
- Papillary (Exophytic) SCC
- Basaloid Squamous Cell Carcinoma
- Viral-Associated Carcinomas (HPV; EBV)
- Adenoid SCC (angiosarcoma-like or acantholytic)
- Adenosquamous Carcinoma
- Lymphoepithelial-like Carcinoma
- Other variants

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) → >2mm 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

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
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

Spindle Cell Squamous Carcinoma
(SCSC)

• Variant of SCC characterized by prominent or even exclusive malignant spindle-shaped cell and/or pleomorphic cells with or without identifiable conventional squamous cell carcinoma component (intraepithelial dysplasia and/or invasive differentiated SCC)
• Synonym: Sarcomatoid carcinoma

Spindle Cell Squamous Carcinoma
Clinical Features

• Uncommon tumor type
• M >> F; primarily occurs in older age groups (6th – 8th decades)
• Sites of occurrence:
  – Larynx (TVC) > oral cavity > cutaneous > tonsil > pharynx, other
• Symptoms vary according to site
• Linked to tobacco and alcohol use/abuse
• No specific correlation with HPV
Spindle cells

Epithelioid cells

Granulation tissue-like appearance
Spindle Cell Squamous Carcinoma
IHC Staining

- Cytokeratins (AE1/AE3, CAM5.2, CK5/6, OSCAR)
- p63, p40
- Vimentin
- Mesenchymal markers (actins, desmin)
Spindle Cell Squamous Carcinoma
Keratin Expression

• 71 of 122 cases (58%) expressed keratin

Spindle Cell Squamous Carcinoma
Epithelial Differentiation

• Identical p53 expression patterns in epithelial and spindle cell components support concept that phenotypically divergent cell populations share similar (epithelial) developmental pathway


Spindle Cell Squamous Carcinoma
Differential Diagnosis

• Sarcomas:
  – heterologous elements may be present in SCSC (e.g., rhabdomyosarcoma, osteosarcoma, chondrosarcoma)
• Inflammatory myofibroblastic tumor
• Reactive processes:
  – myofibroblastic-based
  – Inflammatory (e.g., contact ulcers)
  – post-radiation changes

Spindle Cell Squamous Carcinoma
Association with HPV

• Majority of SCSC not related to HPV
• Rare p16-positive oropharyngeal SCSC harboring HPV identified:
Spindle Cell Squamous Carcinoma
Treatment and Prognosis

- Surgical excision is the treatment of choice
- Adjunctive therapeutic modalities of questionable utility
- Prognosis dependent on clinical stage but overall prognosis is considered to be poor
- Metastasis to regional lymph nodes and to the lungs
- No known ameliorating effect associated with HPV

Papillary Squamous Cell Carcinoma (PSCC)

- Invasive SCC with a predominant papillary (exophytic) growth pattern with thin fibrovascular cores covered by severely dysplastic epithelial cells or immature basaloid cells with minimal or no maturation

PSCC
Clinical Features

- Demographics are similar to those of conventional SCC:
  - men more than women
  - occur in adults with a mean age in the 7th decade of life
- Predilect to the larynx, oral cavity, oro- and hypopharynx, and sinonasal tract:
  - larynx is the most common site of occurrence (0.5% of all laryngeal cancers)
PSCC
Clinical Features Cont’d

- Symptoms vary according to the site of involvement
- Etiology:
  - Alcohol & tobacco
- HPV shown to be important etiologic agent in a subset of PSCC, particularly in the oropharynx
Differential Diagnosis

• Papilloma
• Verrucous Carcinoma

Treatment and Prognosis

• Surgery is the treatment of choice
• Majority are low clinical stage (T2)
• PSCC has a better prognosis than conventional SCC regardless of anatomic subsite
• Lymph node metastasis is uncommon and distant metastasis is rare
• HPV related, p16 positive PSCC of the oropharynx show a trend towards better patient survival than HPV negative PSCC
Basaloid Squamous Cell Carcinoma (BSCC)

- Biologically aggressive histologically high-grade variant of conventional squamous cell carcinoma characterized by invasive growth and predominantly composed of basaloid (pleomorphic) cell population and often limited evidence of squamous cell component

Basaloid Squamous Cell Carcinoma Clinical Features

- M > F; primarily occurs in older age groups (6th – 7th decades)
- Sites of predilection:
  - supraglottic larynx
  - hypopharynx (piriform sinus)
  - oropharynx: base of tongue and tonsil
- Symptoms vary according to site:
  - at presentation tendency to be multifocal, deeply invasive and/or metastatic

Basaloid Squamous Cell Carcinoma Etiology

- Strongly related to alcohol and tobacco
- Non-oropharyngeal BSCC:
  - Transcriptionally-active high risk human papillomavirus (HPV) is consistently absent in BSCC arising outside the oropharynx
Nuclear palisading

Reduplicated basement membrane-like material

Lobular growth, comedonecrosis

BSCC - In Situ Component
BSCC - In Situ Component

BSCC with squamous differentiation

BSCC with squamous differentiation
BSCC with squamous differentiation and clear cells

PAS

DPAS
BSCC with spindle cells

Microcalcifications

Rosettes and Nuclear Palisading
Perineural invasion

Basaloid Squamous Cell Carcinoma
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

Basaloid Squamous Cell Carcinoma
Differential Diagnosis
- Adenoid cystic carcinoma
- Small cell (neuroendocrine) carcinoma
- Conventional squamous cell carcinoma
- Adenosquamous carcinoma
- Spindle cell squamous carcinoma
- Others
**Basaloid Squamous Cell Carcinoma**

**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

**Basaloid Squamous Cell Carcinoma**

- **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)**

**Squamous Cell Lesions**

**Conclusions**

- **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)
Squamous Cell Lesions
Conclusions

• Invasive carcinoma:
  – Diagnostic criteria for microinvasion
  – Findings associated with invasion
  – Simulators of SCC

• Select variants of squamous cell carcinoma:
  – Clinical and pathologic features