Mount Sinai Hospital

Mount Sinai Beth Israel

Premalignant Lesions of the Upper Aerodigestive Tract and Select Variants of Squamous Cell Carcinoma

Arizona Society of Pathologists
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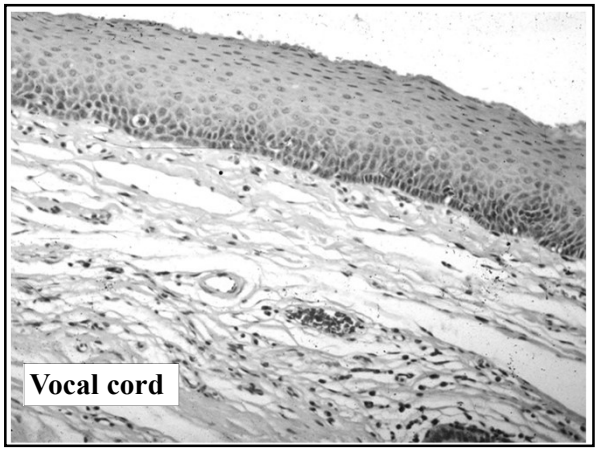
Mount Sinai Roosevelt

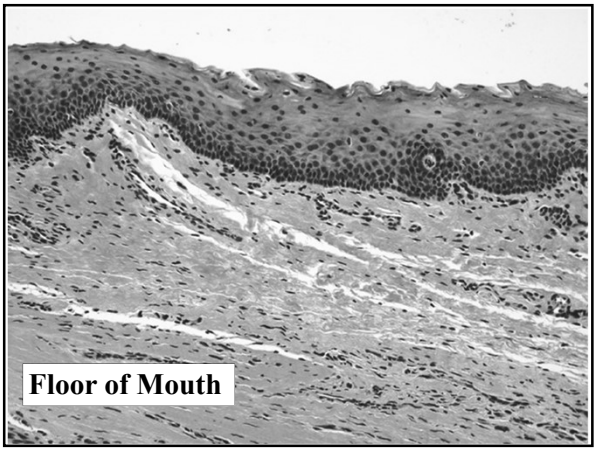
Mount Sinai St. Luke's

Head & Neck Squamous Cell Lesions Outline

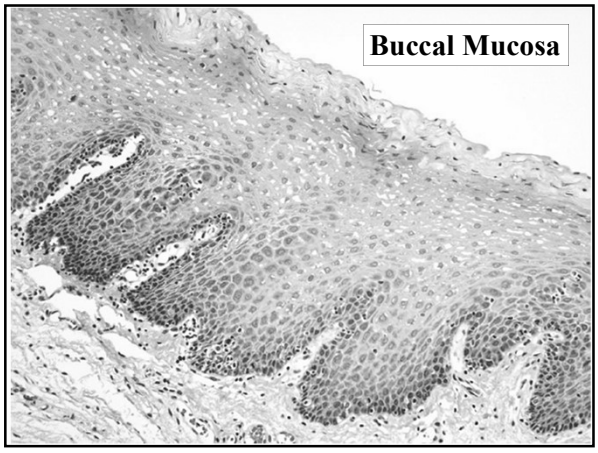
- Keratinizing Dysplasia
- Squamous cell carcinoma:
  - Microinvasive and Invasive
- Select Variants



Vocal cord

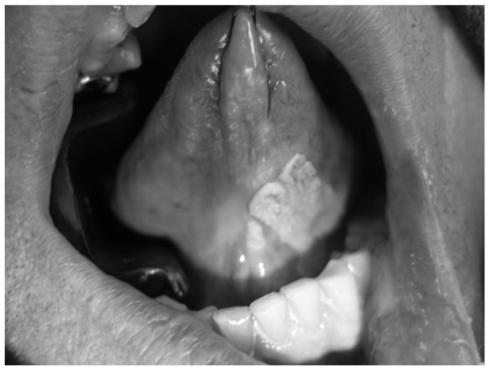


Floor of Mouth

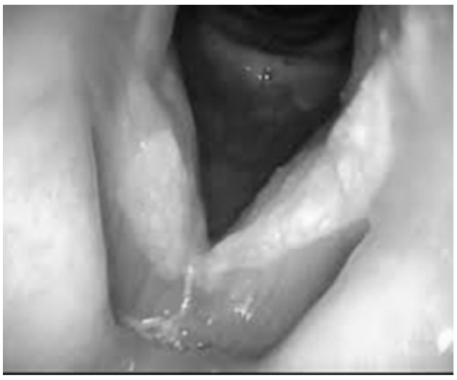


Buccal Mucosa

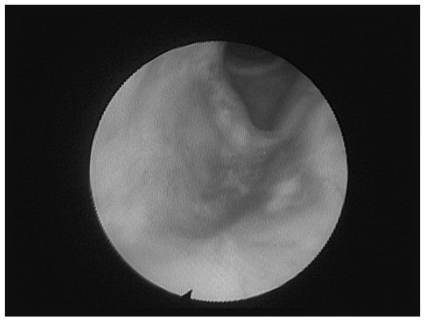
Oral Leukoplakia



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**

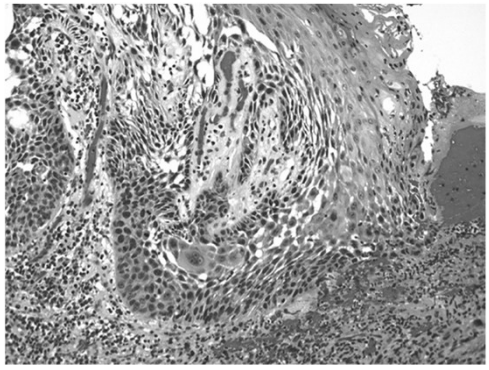
Criteria for Dysplasia 2005 WHO Blue Book

Architecture	Cytology
Irregular epithelial stratification	Abnormal variation in nuclear size (anisonucleosis)
Loss of polarity of basal cells	Abnormal variation in nuclear shape (nuclear pleomorphism)
Drop-shaped rete ridges	Abnormal variation in cell size (anisocytosis)
Increased number of mitotic figures	Abnormal variation in cell shape (cellular pleomorphism)
Abnormally superficial mitoses	Increased nuclear-cytoplasmic ratio
Premature keratinization in single cells (dyskeratosis)	Increased nuclear size
Keratin pearls within rete pegs	Atypical mitotic figures
	Increased number and size of nucleoli
	Hyperchromasia

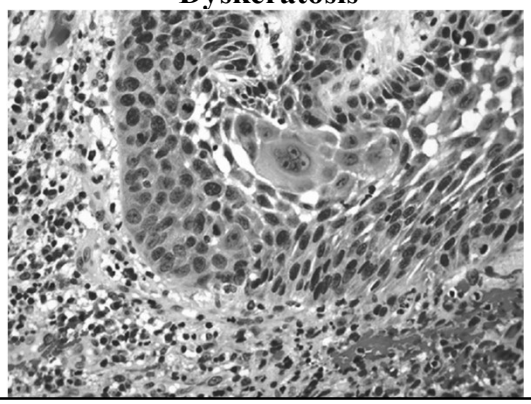
Dyskeratosis

- **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**

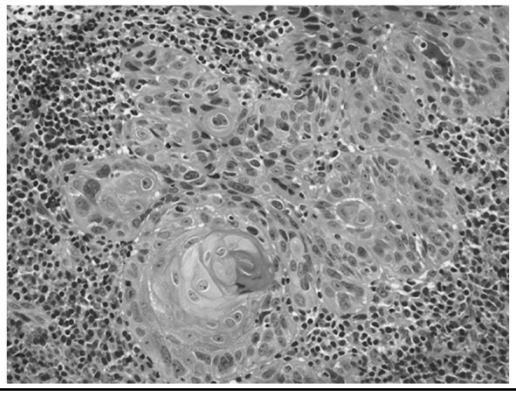
Dyskeratosis



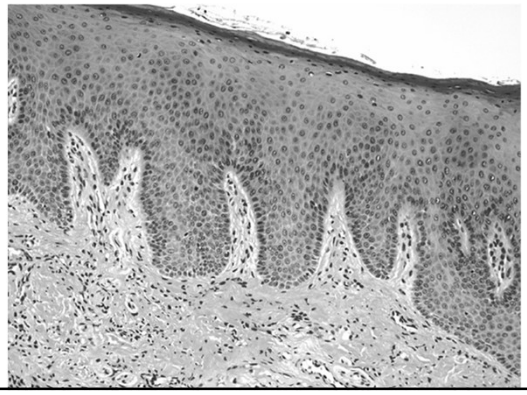
Dyskeratosis



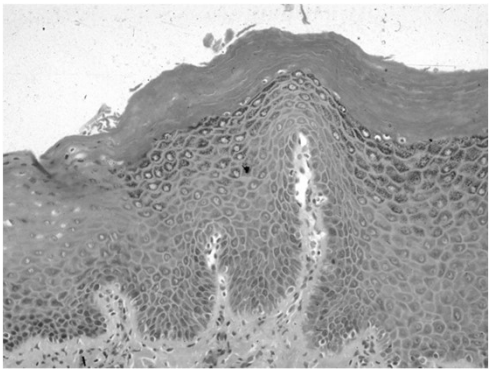
Paradoxical Maturation



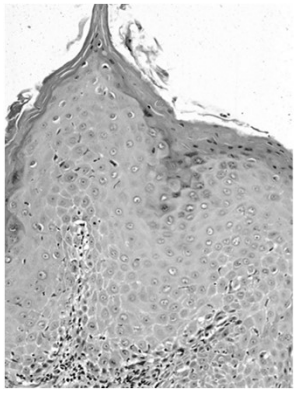
Keratosis without Dysplasia



Keratosis without Dysplasia



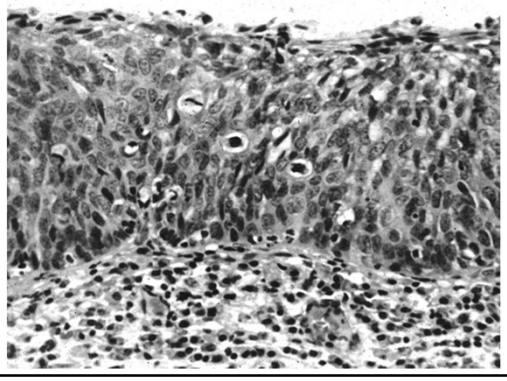
(Papillary or verrucoid) Keratosis without Dysplasia



Upper Aerodigestive Tract Epithelial Dysplasia

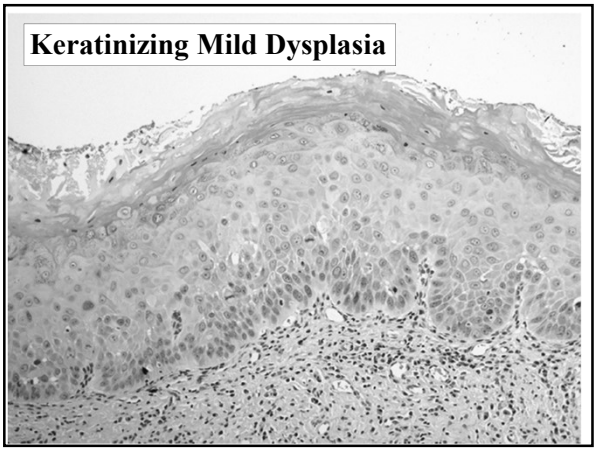
- **"Classic" or Non-Keratinizing:**
  - **Mild dysplasia**
  - **Moderate dysplasia**
  - **Severe dysplasia = Carcinoma in situ**

Carcinoma In Situ

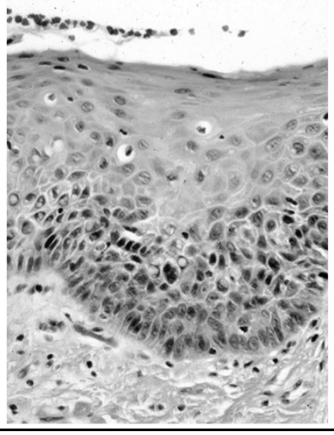


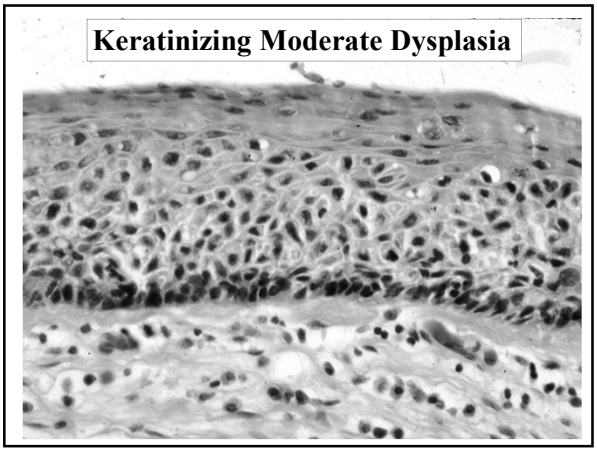
Upper Aerodigestive Tract Epithelial Dysplasia

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

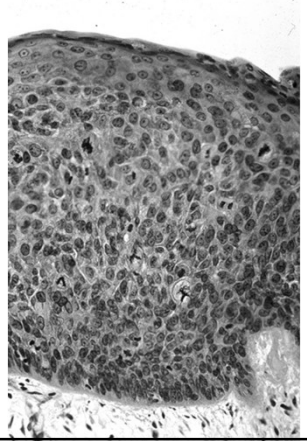


Keratinizing Mild Dysplasia

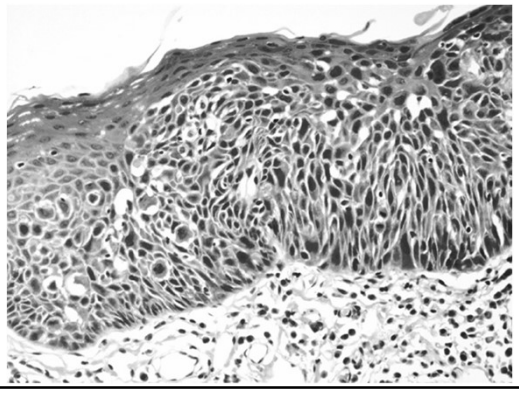




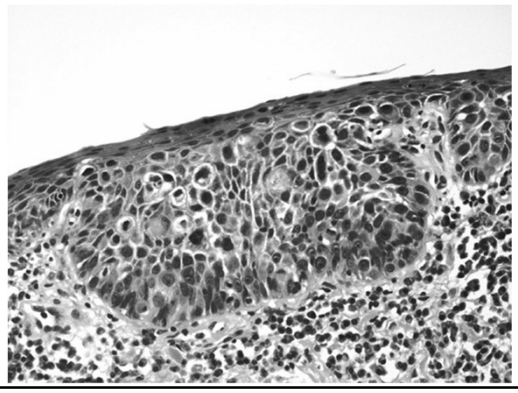
Keratinizing Moderate Dysplasia



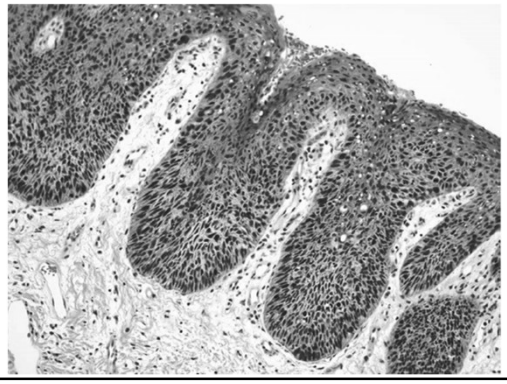
Moderate? Severe? CIS?



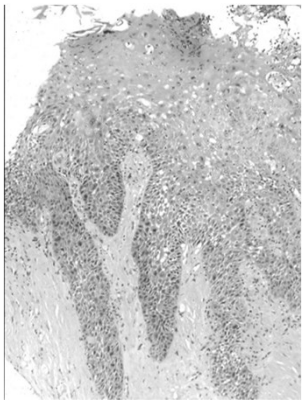
Moderate? Severe? CIS?



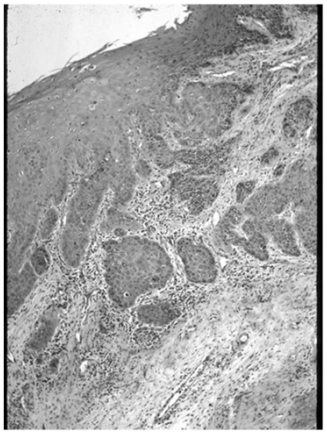
Moderate? Severe? CIS?



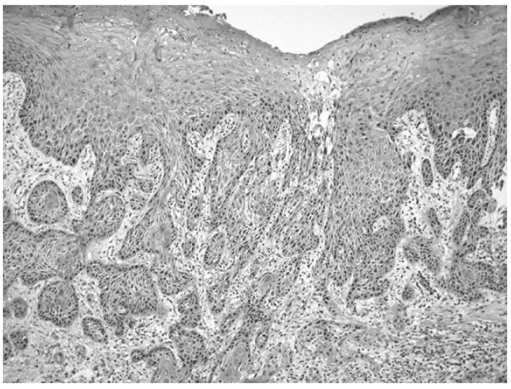
Moderate?
Severe?
CIS?



"Drop Off" 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**

2005 WHO Classification

2005 WHO Classification	Squamous Intraepithelial Neoplasia (SIN)	Ljubljana Classification Squamous Intraepithelial Lesions (SIL)
Squamous cell hyperplasia		Squamous cell (Simple) hyperplasia
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia*
Moderate dysplasia	SIN 2	Atypical hyperplasia**
Severe dysplasia	SIN 3***	Atypical hyperplasia**
Carcinoma in-situ	SIN 3***	Carcinoma in-situ

* Basal/parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter the lower grade of precursor lesions.
** 'Risky epithelium'. The analogy to moderate and severe dysplasia is approximate.
*** The advocates of SIN combine severe dysplasia and carcinoma in-situ.

Incidence of Invasive Carcinoma Developing in Patients with Keratosis Without Atypia

Author (yr)	Total number of cases	Number of invasive carcinomas	% of all cases
McGavran (1960)	66	1	1.5
Norris (1963)	30	1	3.3
Gabriel (1973)	50	3	6
Henry (1979)	29	1	3.4
Crissman (1979)	50	0	0
Hellquist (1982)	98[a]	2	2
Gillis (1983)	7	2	28.6
Kalter (1987)	38	2	5.3
Sllamniku (1989)	604	18	3
Hojslet (1989)	128[a]	6	4.7
Blackwell (1995)	6	0	0
Total	1106	36 (3.3%)	5.25 (average)

[a]Includes some patients with mild atypia.
Source: Sec. IX, Refs. 1–4, 7, 9–14.

Incidence of Invasive Carcinoma Developing in Patients with Keratosis with Atypia

Author (yr)	Total number of cases	Number of invasive carcinomas	% of all cases
McGavran (1960)	18	2	11.1
Norris (1963)	86	5	5.8
Gabriel (1973)	55	4	7.3
Henry (1979)	14	3	21.4
Crissman (1979)	42	3	7.1
Hellquist (1982)	63[a]	12	19
Gillis (1983)	17	5	29.4
Kalter (1987)	92	20	21.7
Sllamniku (1989)	317	44	13.9
Hojslet (1989)	19	8	42.1
Blackwell (1995)	50	12	24
Total	773	118 (15.3%)	18.4 (average)

[a]Includes only grade II and III atypia.
Source: Sec. IX, Refs. 1–4, 7, 9–14.

Incidence of Invasive Carcinoma in Patients with Keratosis with Mild, Moderate, and Severe Atypia

Author (yr)	Mild (Carcinomas: total cases)	Moderate (Carcinomas: total cases)	Severe (Carcinomas: total cases)
Hellquist (1982)	2:98[a]	3:24	9:39[b]
Sllamniku (1989)	15:204	4:23	25:90
Hojslet (1989)	6:128[a]	4:9	4:10
Blackwell (1995)	3:26	5:15	4:9
Total	26:456	16:71	42:148
	(5.7%)	(22.5%)	(28.4%)

[a]Includes some cases of keratosis without atypia.
[b]Includes some cases of carcinoma in situ.
Source: Sec. IX, Refs. 2, 3, 13, 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**

2016-17 WHO Classification for Intraepithelial Dysplasia 2 Tier Grading

- **Low-grade dysplasia (to include previous category of mild dysplasia):**
  - **low malignant potential**
  - **spectrum of morphological changes ranging from squamous hyperplasia up to an augmentation of basal and parabasal cells occupying up to the lower half of the epithelium, while the upper portion retains maturation**

2016-17 WHO Classification for Intraepithelial Dysplasia 2 Tier Grading

- **High-grade dysplasia (to include previous categories of moderate dysplasia, severe dysplasia, and carcinoma in situ):**
  - **pre-malignant lesion**
  - **spectrum of changes including immature epithelial cells occupying the lower half up to the whole epithelial thickness**

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**

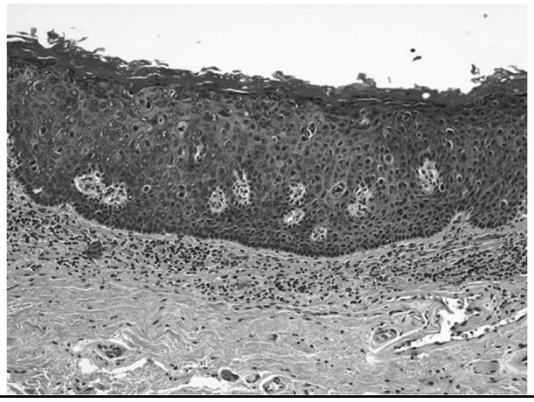
***Woo SB, et al. Modern Pathol 2013;26:1288-97**

Oral Dysplasia and HR-HPV

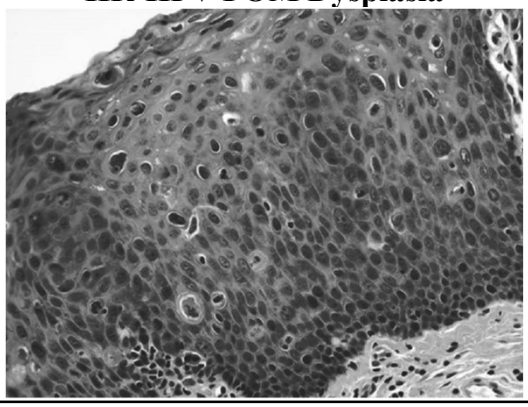
- HR-HPV associated with a subset of severe epithelial dysplasia or carcinoma in situ characterized by:
  - Most adult men; ventral tongue or FOM
  - Diffuse loss of squamous differentiation & high proliferation index throughout basal and suprabasal epithelial layers
- Identified by p16 IHC staining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

McCord C, et al. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:541-9

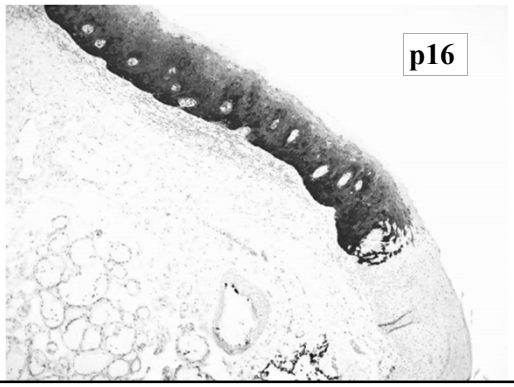
HR-HPV FOM Dysplasia



HR-HPV FOM Dysplasia



HR-HPV FOM Dysplasia

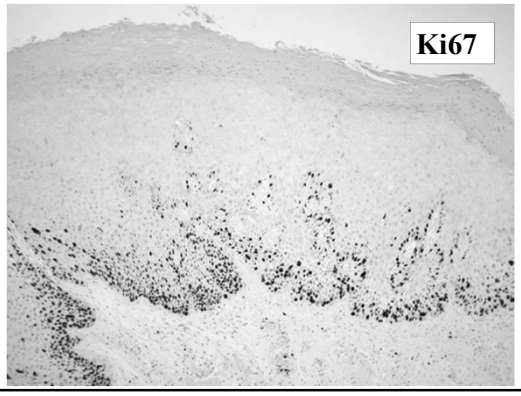


Keratinizing Dysplasia

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

High-Grade Keratinizing Dysplasia



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

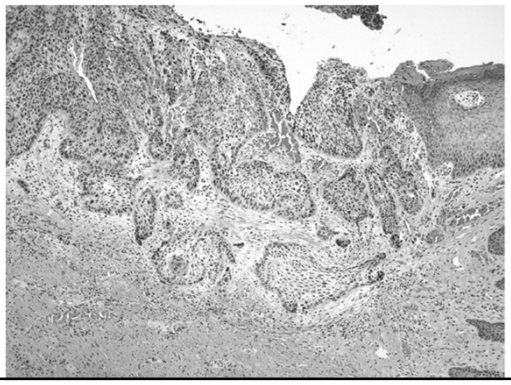
Squamous Cell Carcinoma Microinvasive Carcinoma (MIC)

- 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

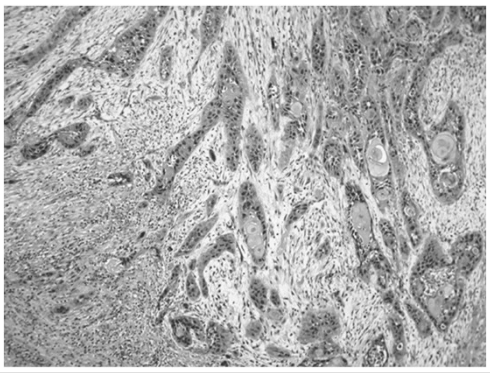
Invasive SCC Diagnostic Features

- 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

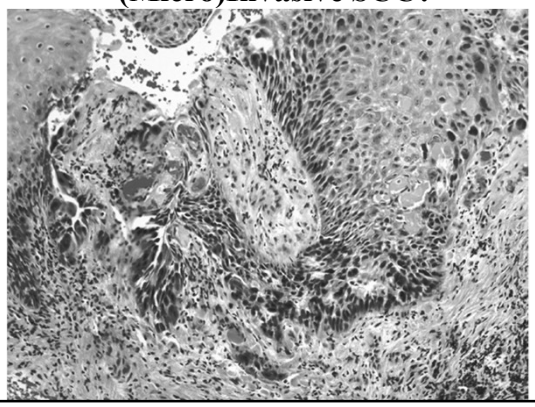
Invasive SCC



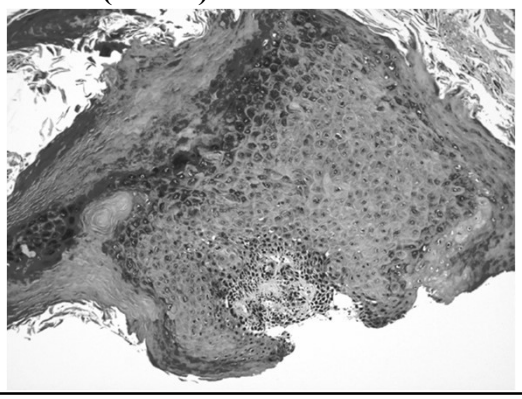
Invasive SCC



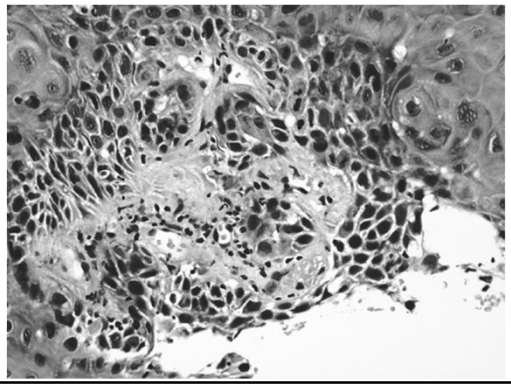
(Micro)Invasive SCC?



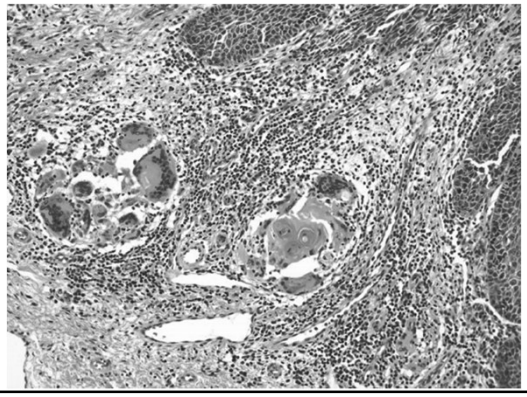
(Micro)Invasive SCC?



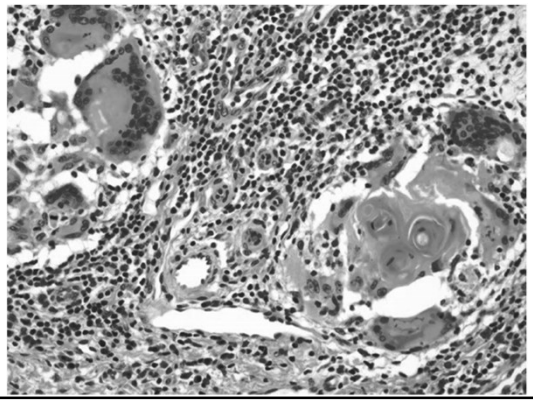
(Micro)Invasive SCC?



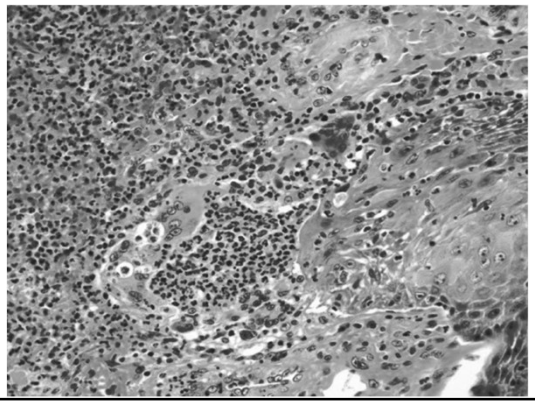
Keratin Granuloma

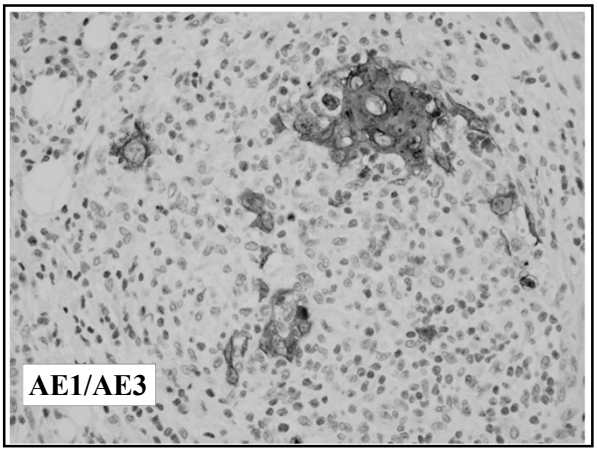


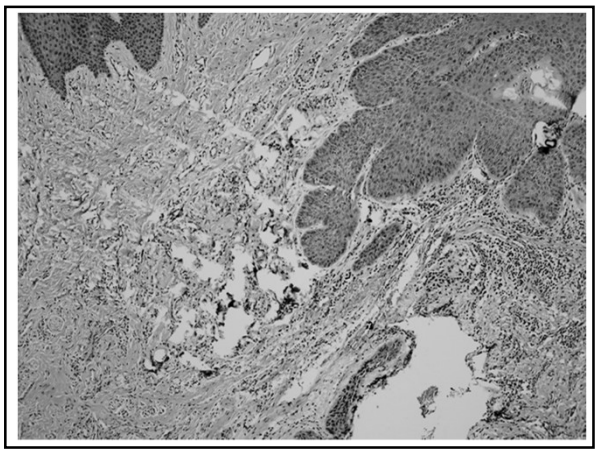
Keratin Granuloma

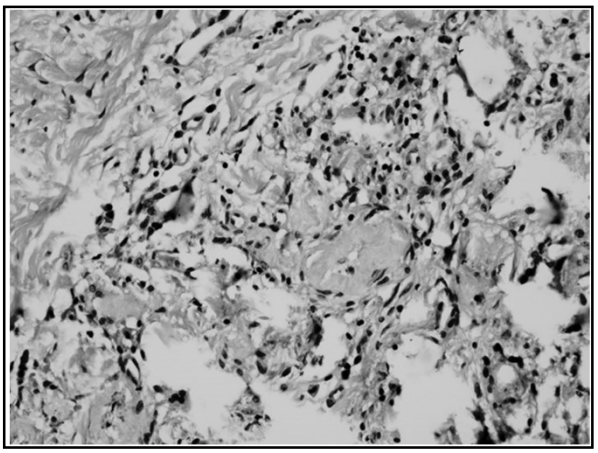


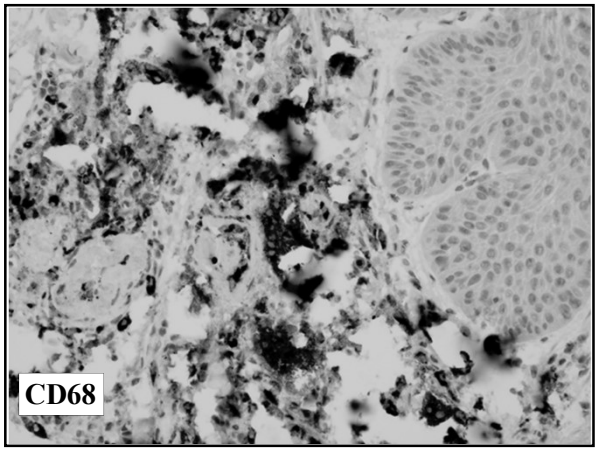
Keratin Granuloma

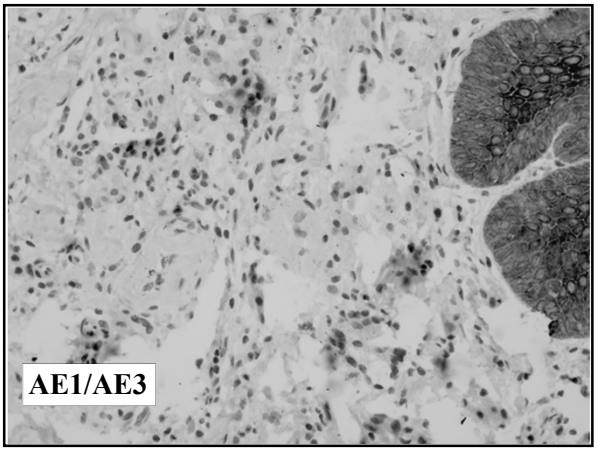








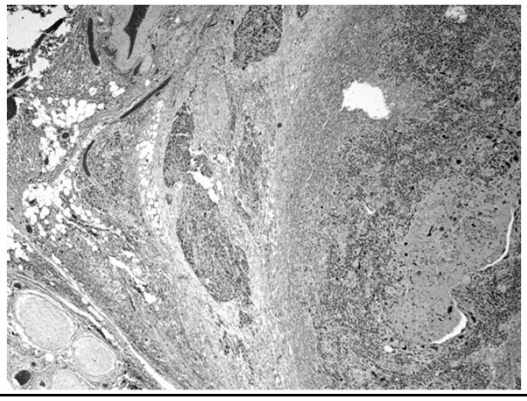




HNSCC
Factors Associated with Prognosis

- **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**

Extranodal Extension



Variants of Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Squamous Cell Carcinoma Variants

- Verrucous Carcinoma
- Papillary (Exophytic) SCC
- Spindle Cell Squamous Carcinoma
- 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)

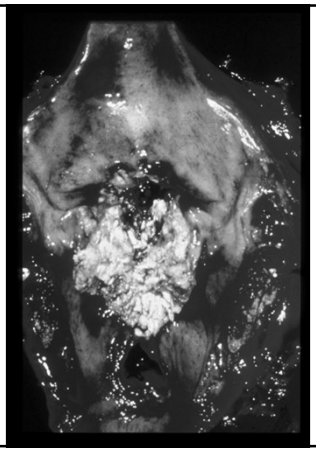
- Highly differentiated variant of squamous cell carcinoma with locally destructive but not metastatic capabilities

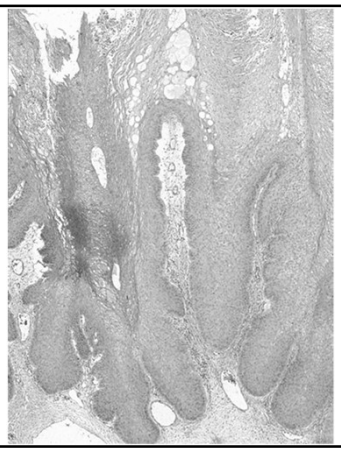
Verrucous Carcinoma Clinical Features

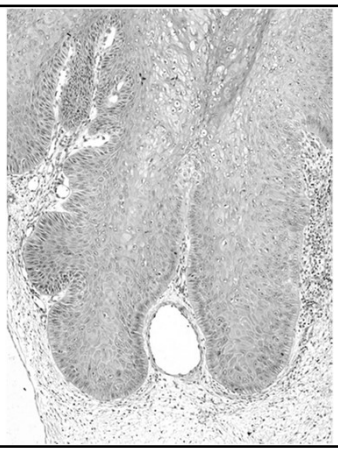
- M > F; generally occurs in older age groups (6^{th} – 7^{th} decades of life)
- Sites:
  - oral cavity (4%) > larynx (1-3%) > other (sinonasal tract; nasopharynx)
- Symptoms vary according to site

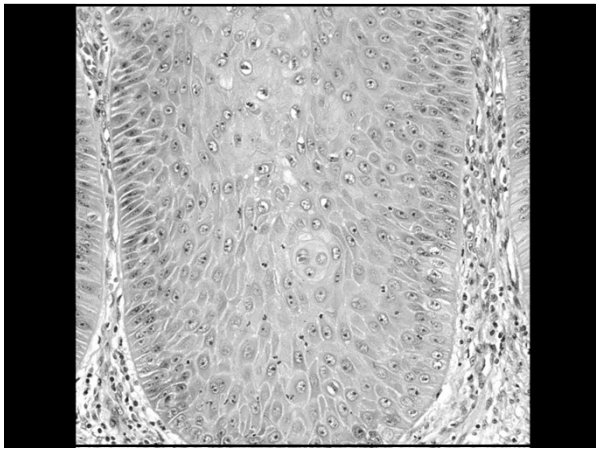
Verrucous Carcinoma Etiology

- 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





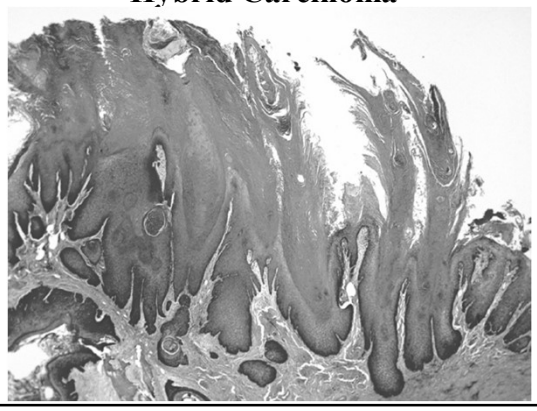




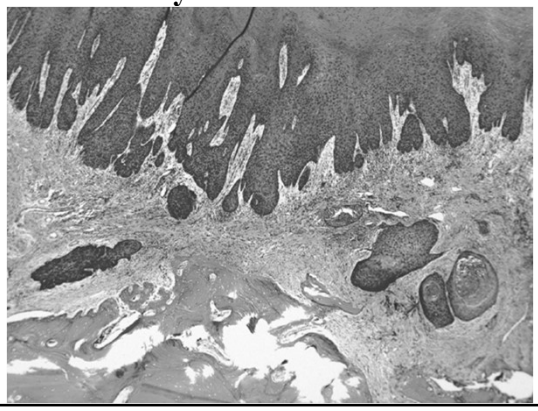
Hybrid Carcinoma

- 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

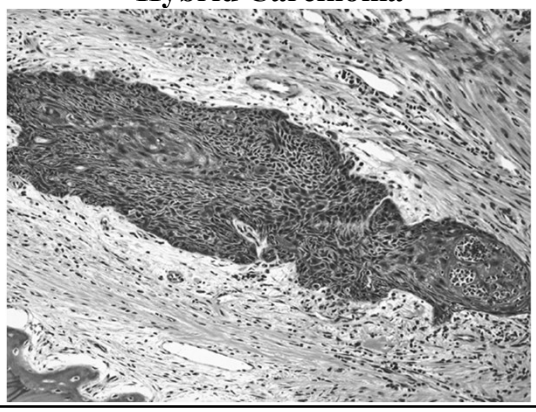
Hybrid Carcinoma



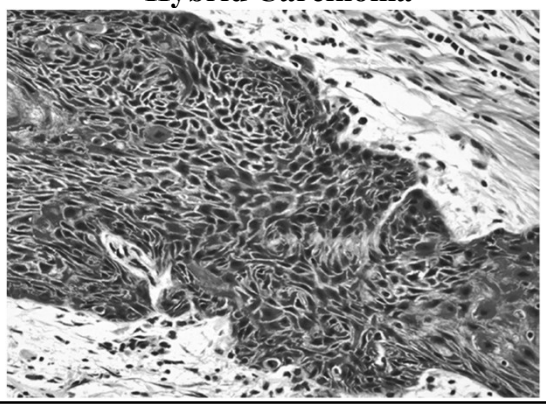
Hybrid Carcinoma



Hybrid Carcinoma



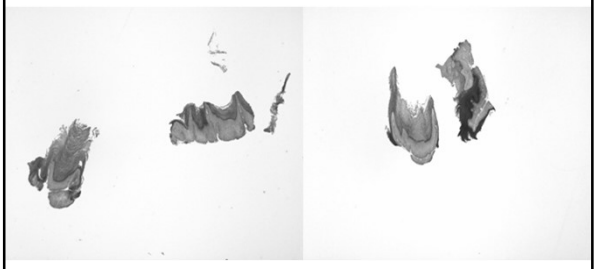
Hybrid Carcinoma



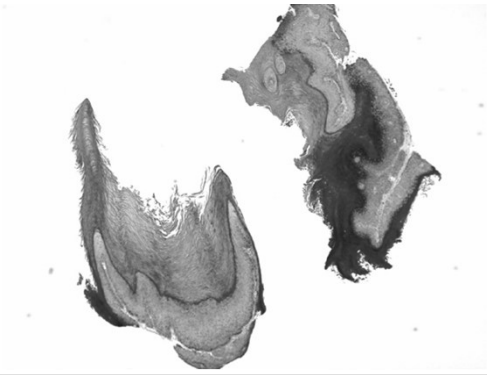
Hybrid Carcinoma vs VC with Dysplasia or Minimal Invasion

- **Patel KR, et al. Head Neck Pathol 2015;9:65-73**:
  - **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**

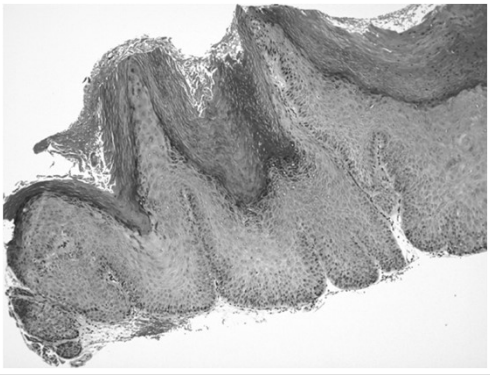
Biopsy Diagnosis of Verrucoid Lesions



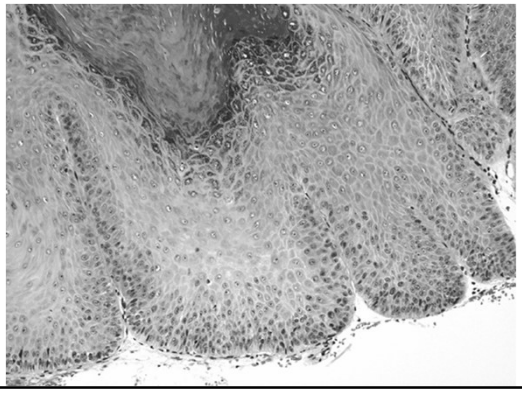
Biopsy Diagnosis of Verrucoid Lesions



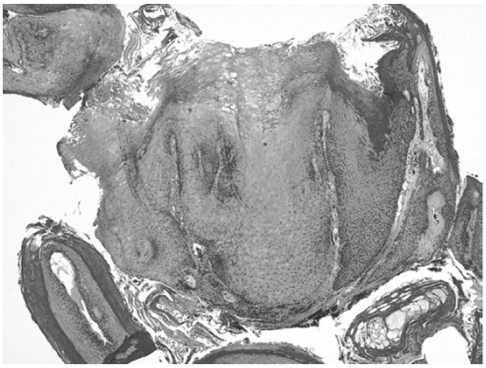
Biopsy Diagnosis of Verrucoid Lesions



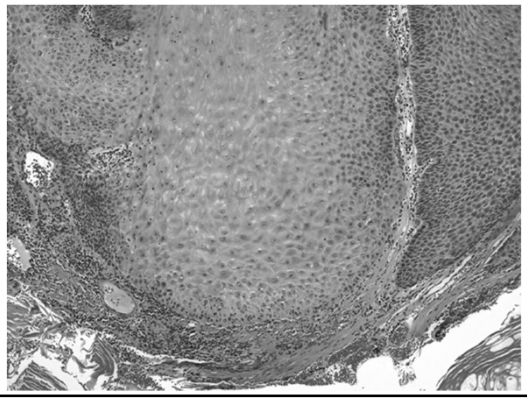
Biopsy Diagnosis of Verrucoid Lesions



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

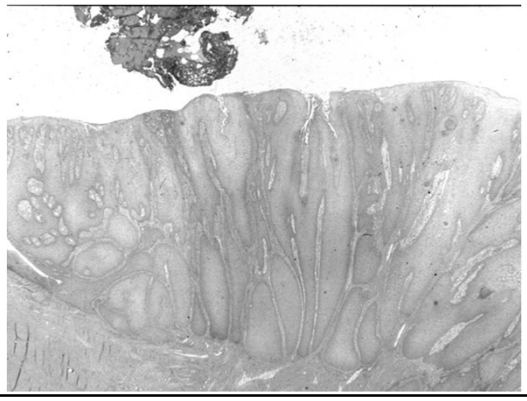
Verrucous Carcinoma Biopsy Diagnosis

- "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



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

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

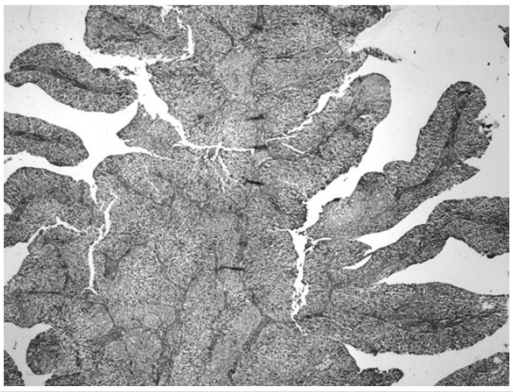
PSCC Clinical Features

- 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

PSCC



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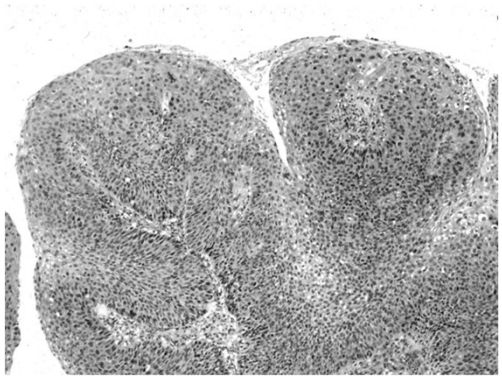

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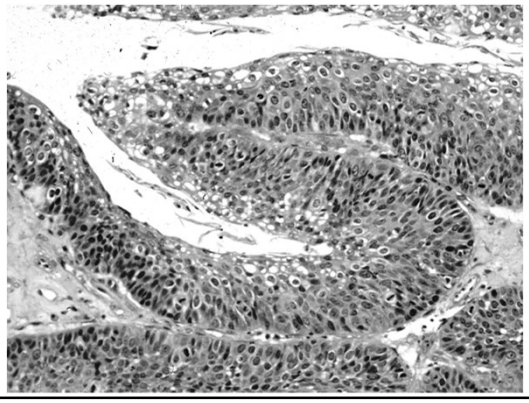

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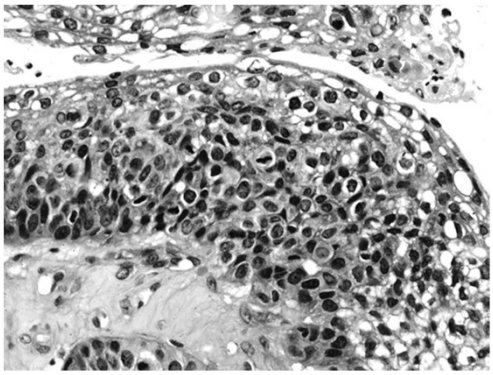

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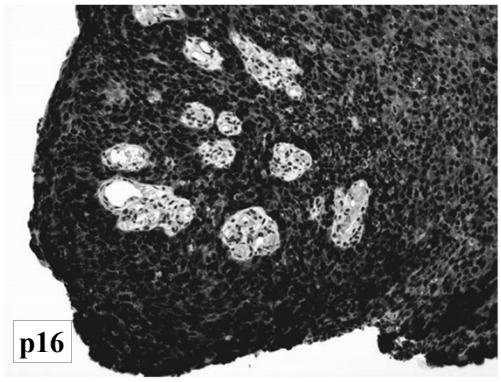

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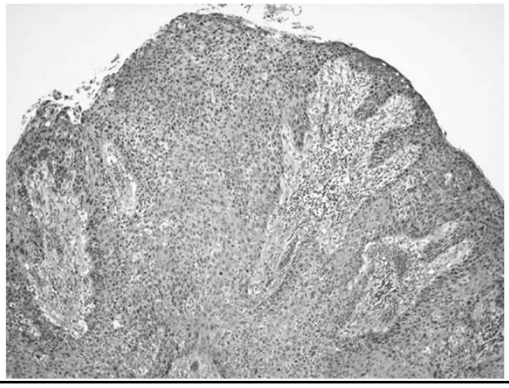

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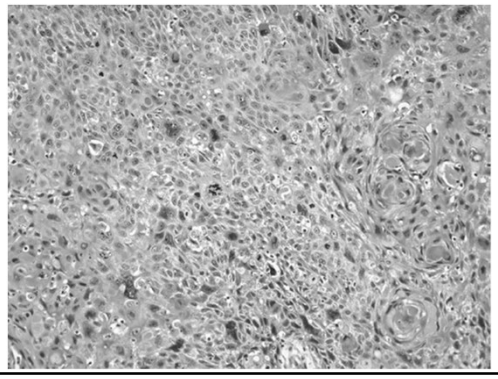

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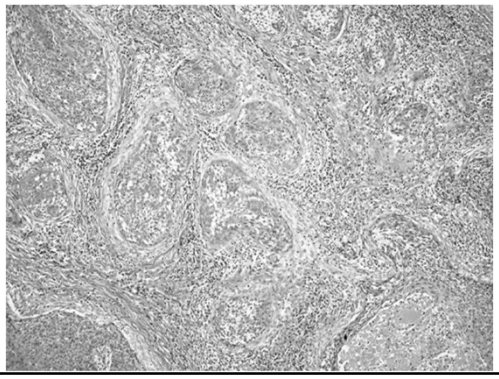


PSCC
Differential Diagnosis

- Papilloma
- Verrucous Carcinoma

PSCC
Treatment and Prognosis

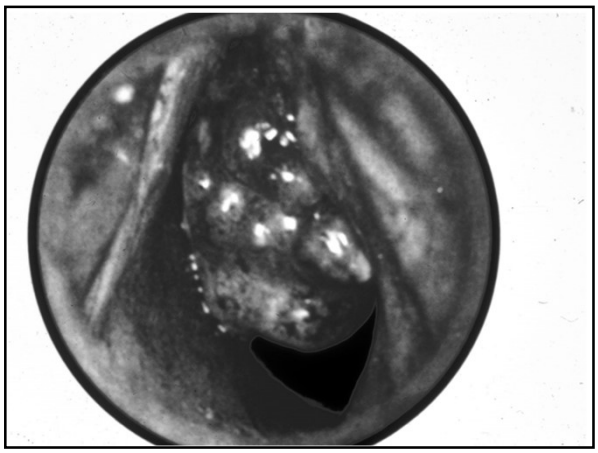
- Surgery is the treatment of choice
- Majority are low clinical stage (T2)
- PSCC has a better prognosis than conventional SCC regardless of anatomic subsite
- Lymph node metastasis is uncommon and distant metastasis is rare
- HPV related, p16 positive PSCC of the oropharynx show a trend towards better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

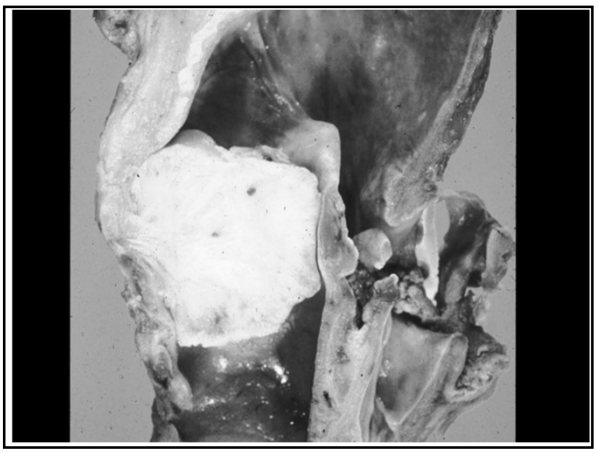
Spindle Cell Squamous Carcinoma (SCSC)

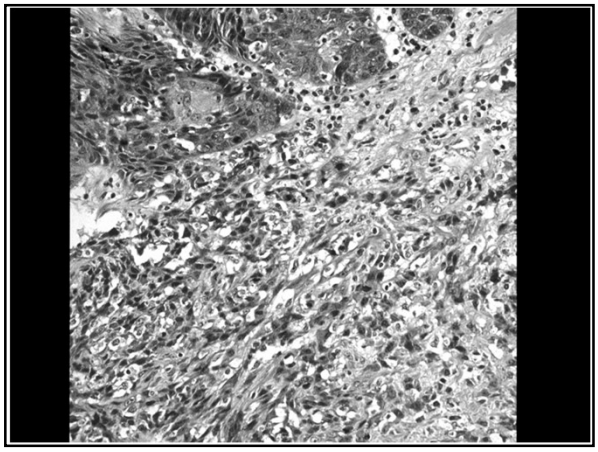
- Variant of SCC characterized by prominent or even exclusive malignant spindle-shaped cell and/or pleomorphic cells with or without identifiable conventional squamous cell carcinoma component (intraepithelial dysplasia and/or invasive differentiated SCC)
- Synonym: Sarcomatoid carcinoma

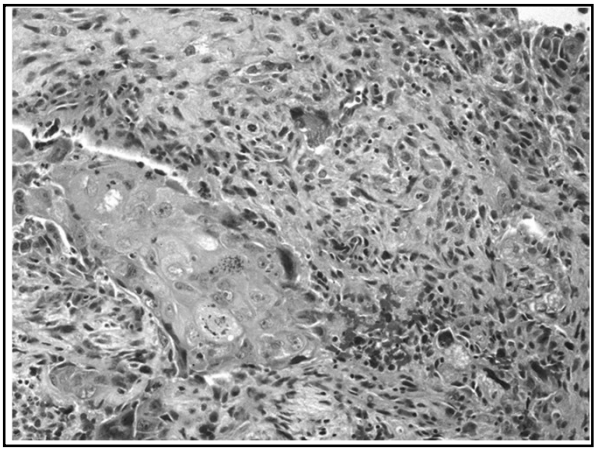
Spindle Cell Squamous Carcinoma
Clinical Features

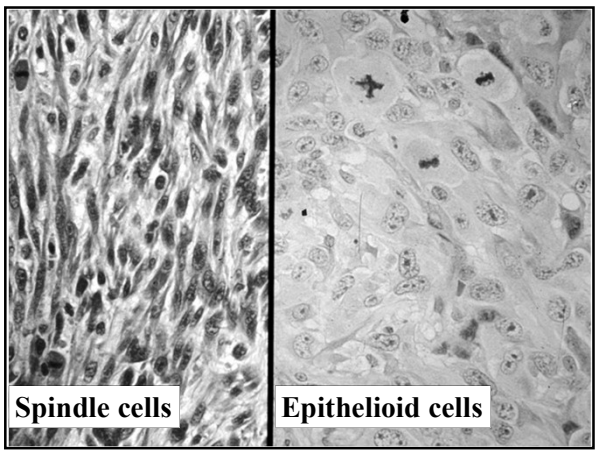
- Uncommon tumor type
- M >> F; primarily occurs in older age groups (6^{th} – 8^{th} decades)
- Sites of occurrence:
  - Larynx (TVC) > oral cavity > cutaneous > tonsil > pharynx, other
- Symptoms vary according to site
- Linked to tobacco and alcohol use/abuse
- No specific correlation with HPV

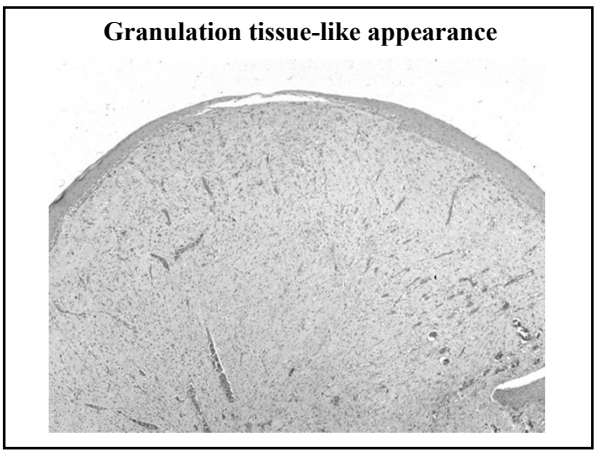


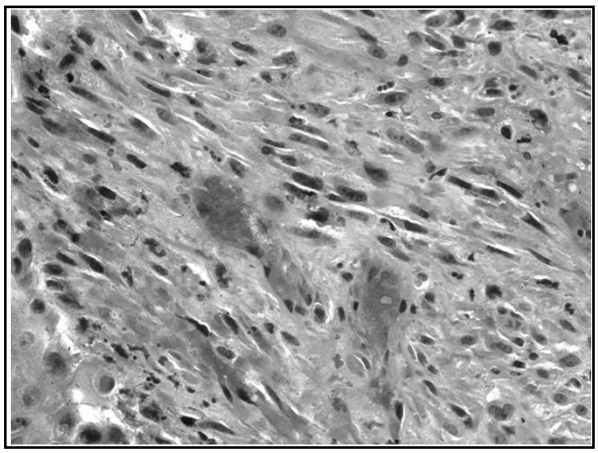


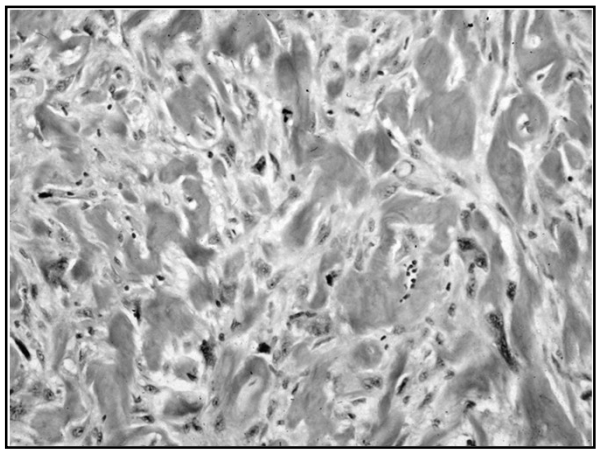


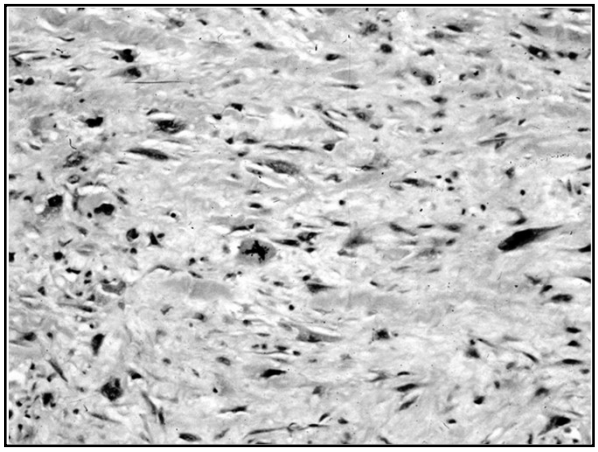



Spindle cells
Epithelioid cells


Granulation tissue-like appearance

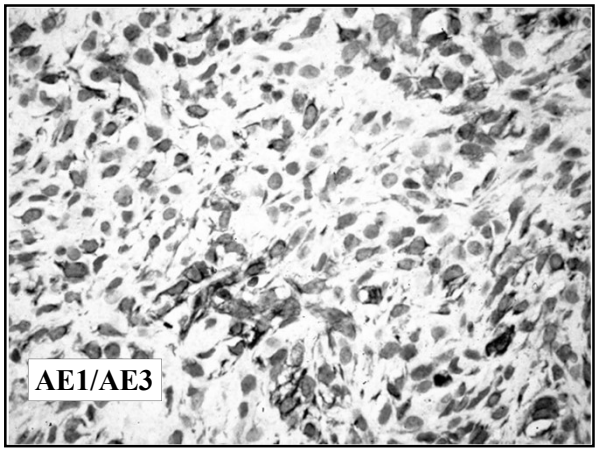


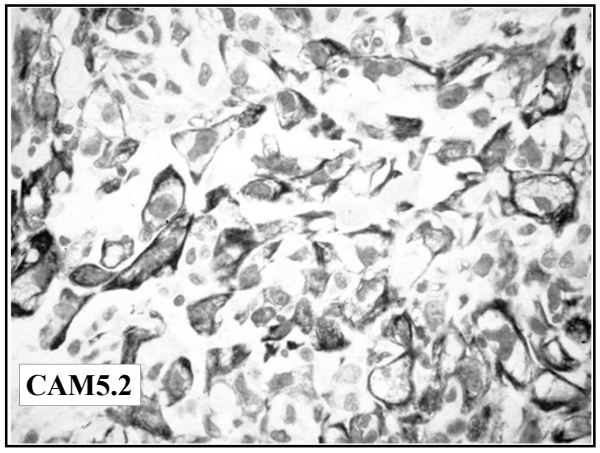


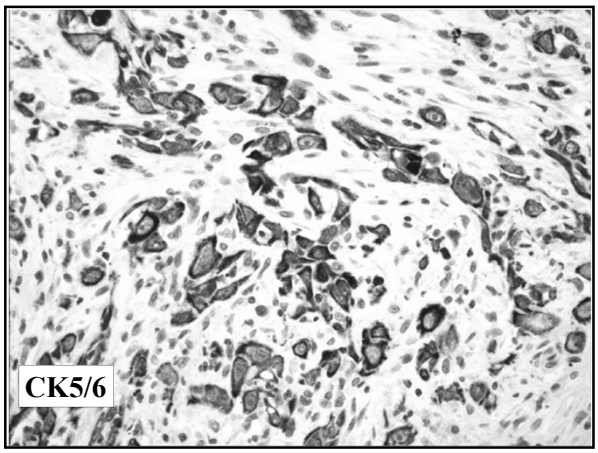


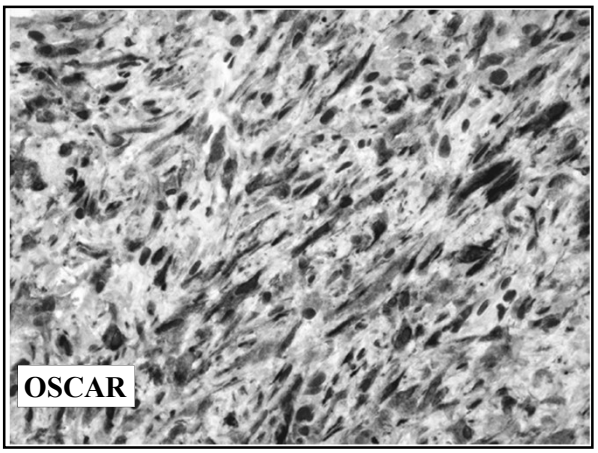
Spindle Cell Squamous Carcinoma IHC Staining

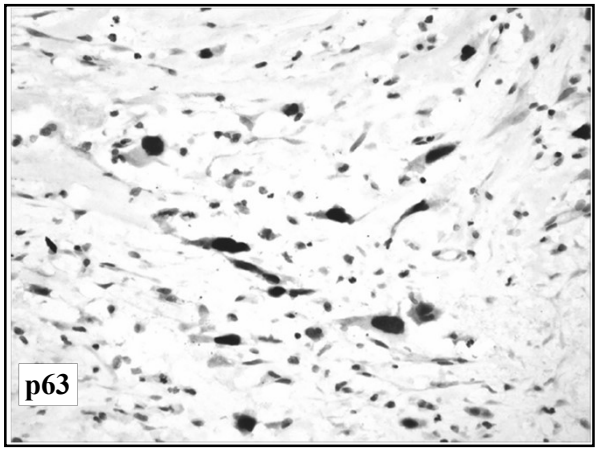
- **Cytokeratins (AE1/AE3, CAM5.2, CK5/6, OSCAR)**
- **p63, p40**
- **Vimentin**
- **Mesenchymal markers (actins, desmin)**







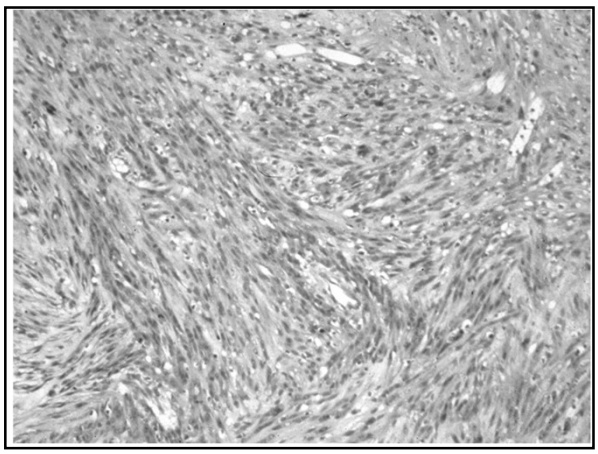


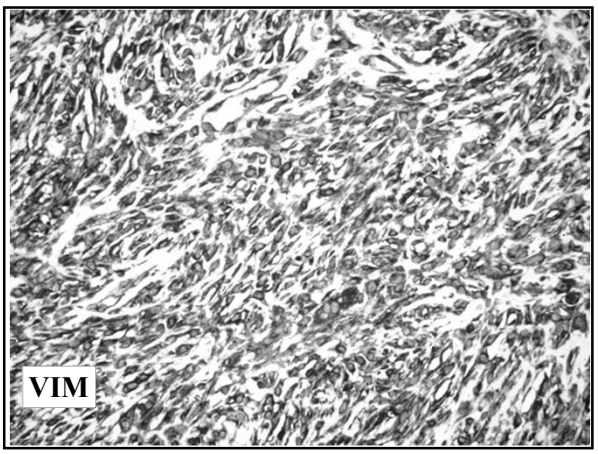


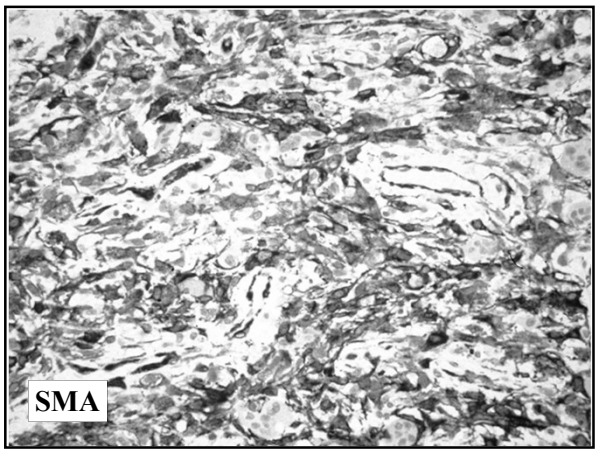
Spindle Cell Squamous Carcinoma Keratin Expression

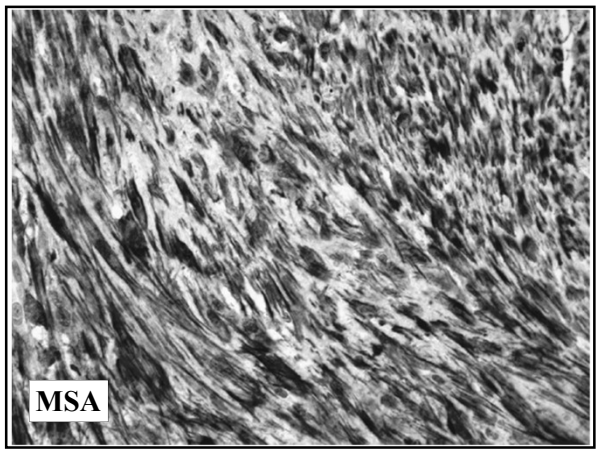
- **71 of 122 cases (58%) expressed keratin**

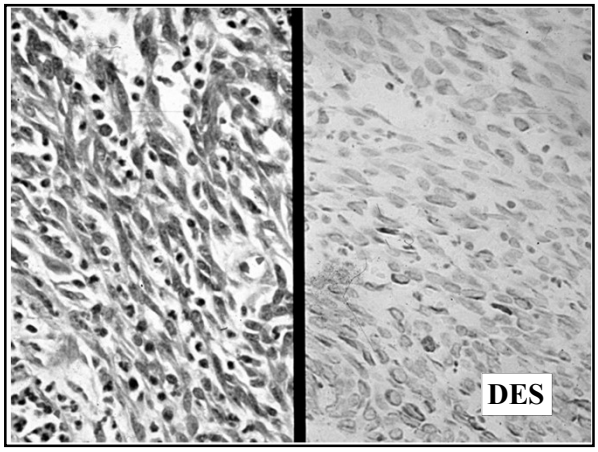
Lewis J, et al. Hum Pathol 1997;28:664-73











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

Ansari-Lari MA, et al. Am J Surg Pathol 2002;26:1024-31

Spindle Cell Squamous Carcinoma Differential Diagnosis

- Sarcomas:
  - heterologous elements may be present in SCSC (benign/malignant bone, cartilage; skeletal muscle (RMS)
- 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:
  - Watson RF, Chernock RD, Wang X, Liu W, Ma XJ, Luo Y, Wang H, El-Mofty SK, Lewis JS Jr. Head Neck Pathol 2013;7:250-257

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

Basaloid Squamous Cell Carcinoma (BSCC)

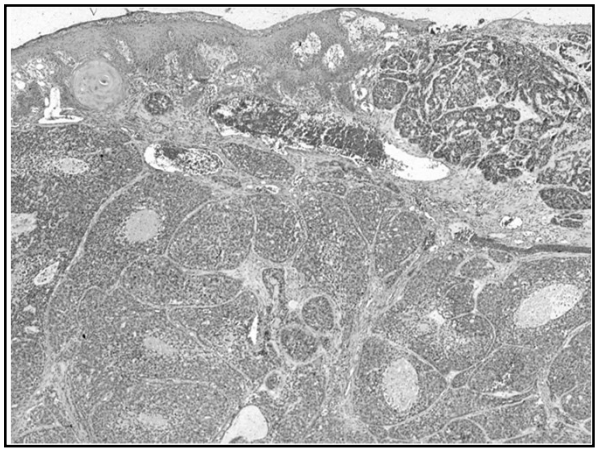
- Biologically aggressive histologically high-grade variant of conventional squamous cell carcinoma characterized by invasive growth and predominantly composed of basaloid (pleomorphic) cell population and often limited evidence of squamous cell component

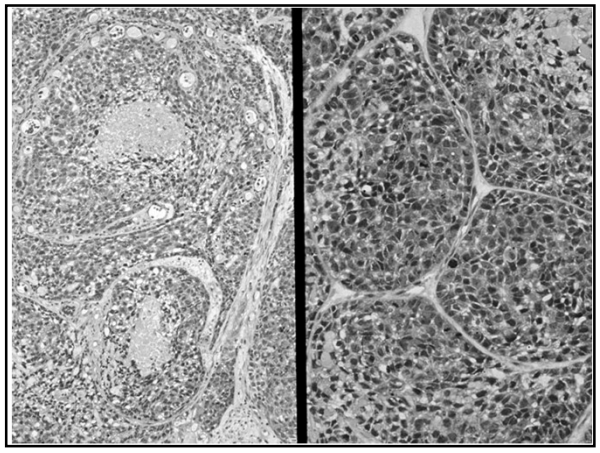
BSCC Clinical Features

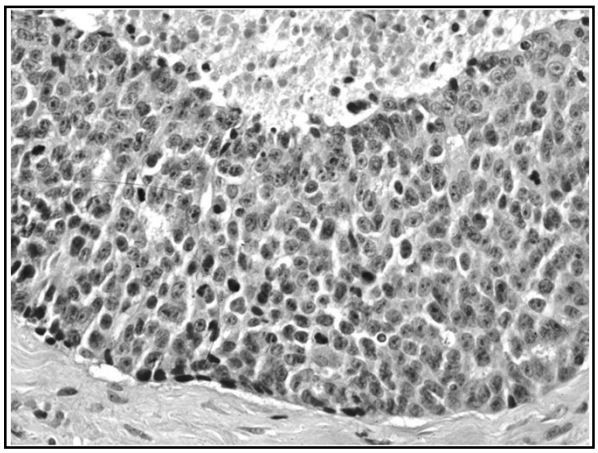
- M > F; primarily occurs in older age groups (6^{th} – 7^{th} decades)
- Sites of predilection:
  - supraglottic larynx; hypopharynx (piriform sinus); oropharynx (base of tongue and tonsil)
- Symptoms vary according to site:
  - at presentation tendency to be multifocal, deeply invasive and/or metastatic

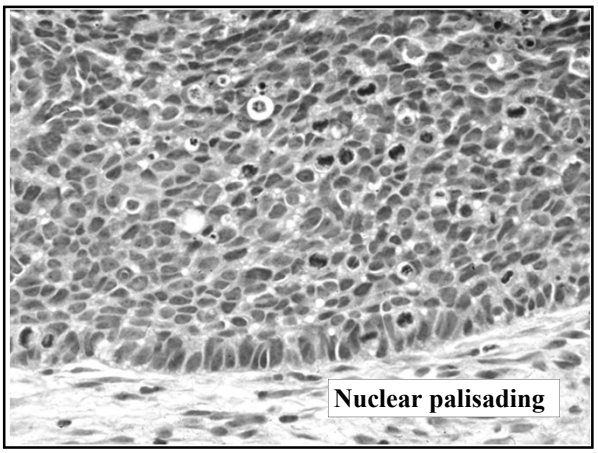
BSCC Etiology

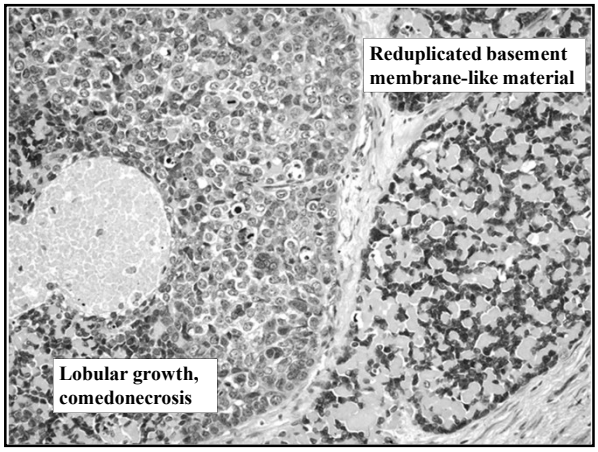
- Strongly related to alcohol and tobacco
- Non-oropharyngeal BSCC:
  - Transcriptionally-active high risk human papillomavirus (HPV) is consistently absent in BSCC arising outside the oropharynx

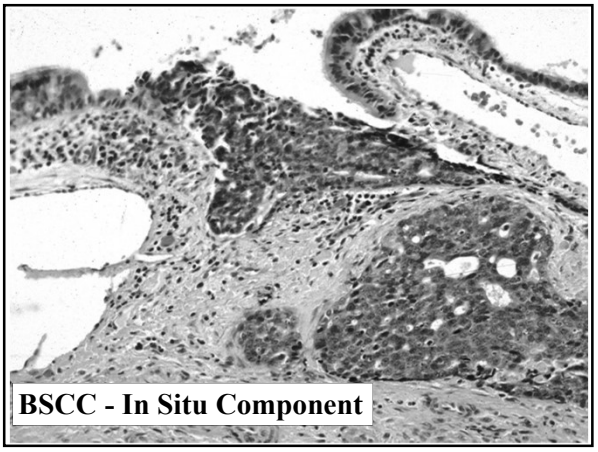


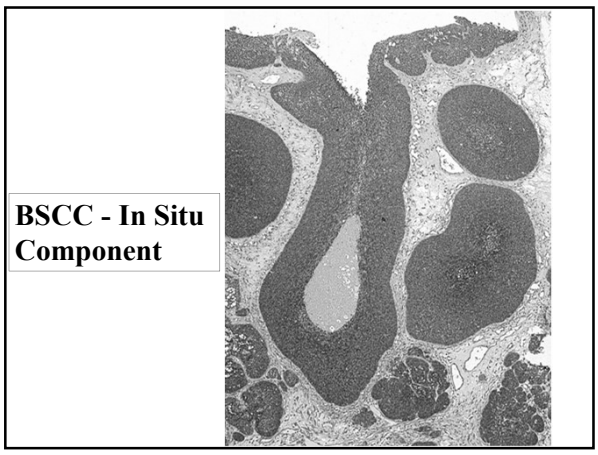


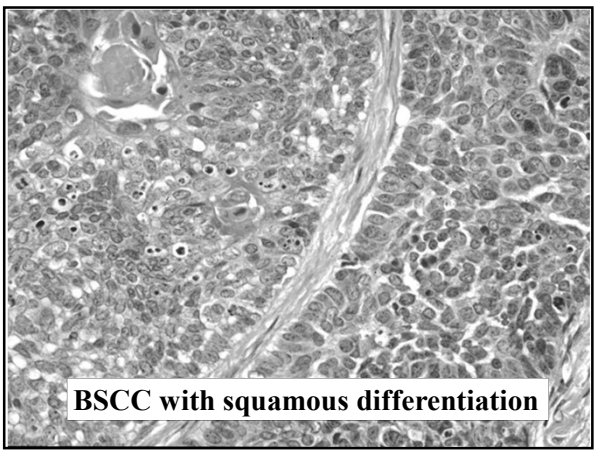


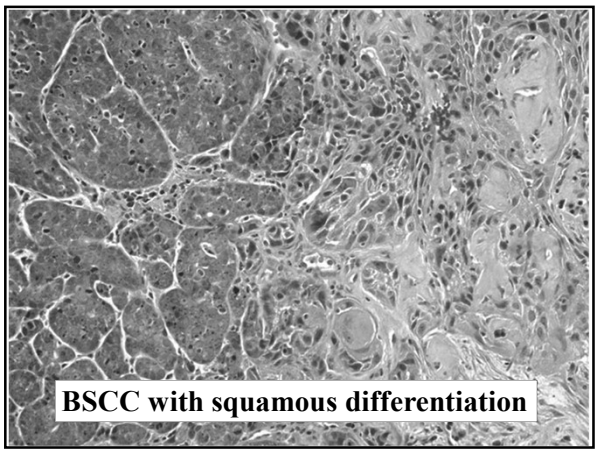

Nuclear palisading

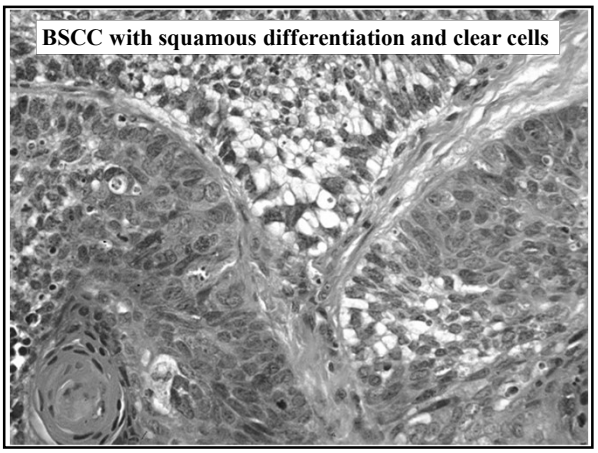

Reduplicated basement membrane-like material
Lobular growth, comedonecrosis

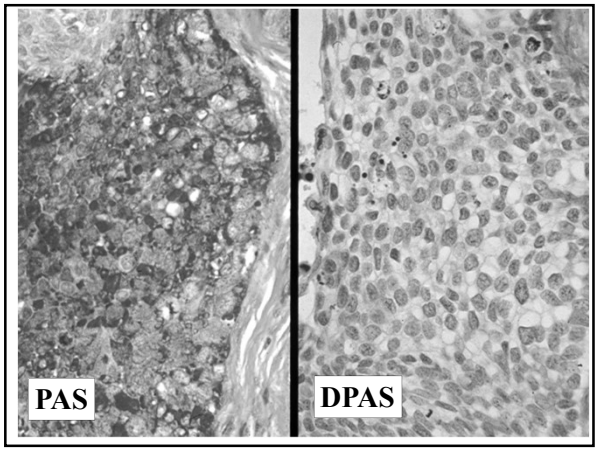

BSCC - In Situ Component

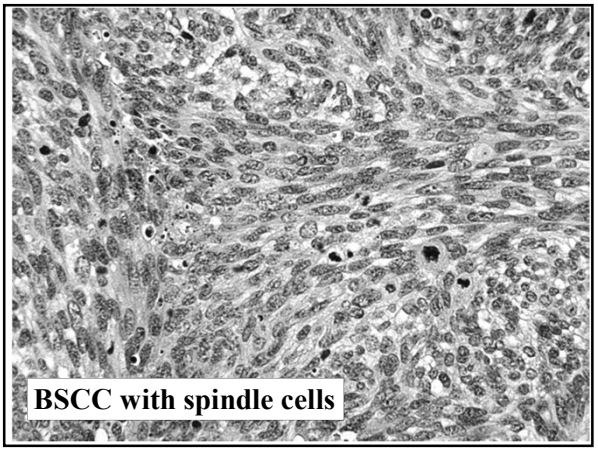

BSCC - In Situ Component

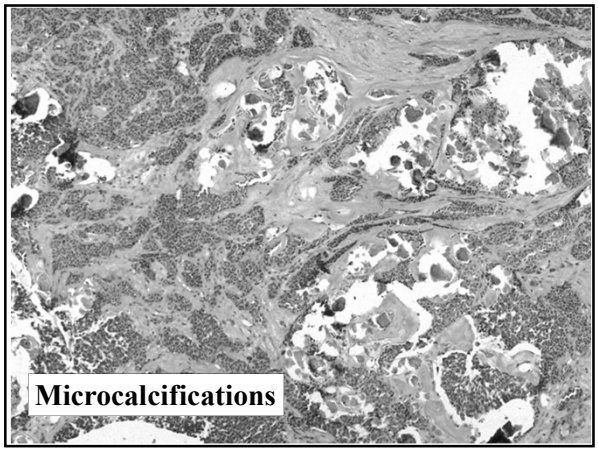

BSCC with squamous differentiation

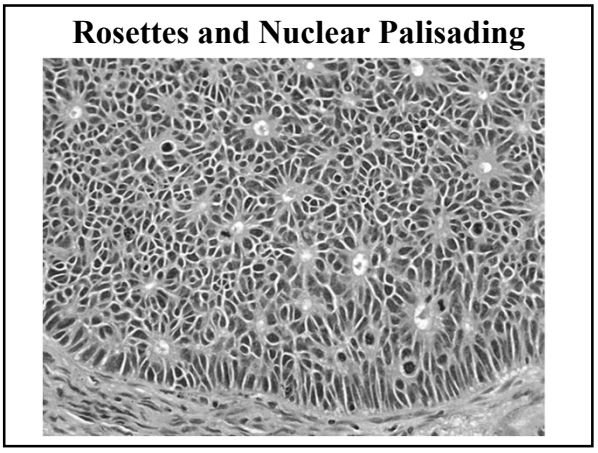

BSCC with squamous differentiation

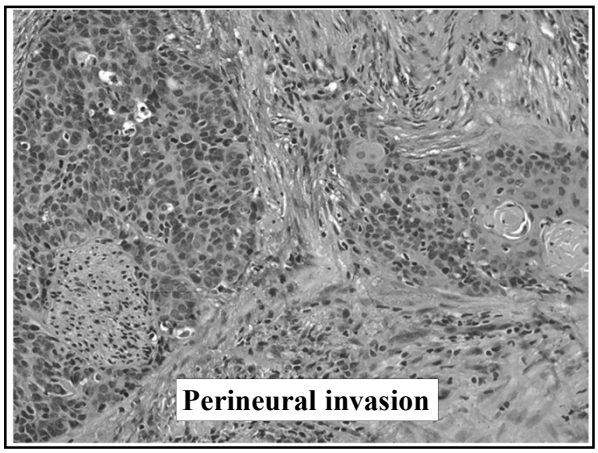

BSCC with squamous differentiation and clear cells


PAS
DPAS


BSCC with spindle cells


Microcalcifications


Rosettes and Nuclear Palisading



BSCC
IHC Findings

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

BSCC
Differential Diagnosis

- Adenoid cystic carcinoma
- Small cell (neuroendocrine) carcinoma
- Conventional squamous cell carcinoma
- Adenosquamous carcinoma
- Spindle cell squamous carcinoma
- Others

BSCC
Treatment and Prognosis

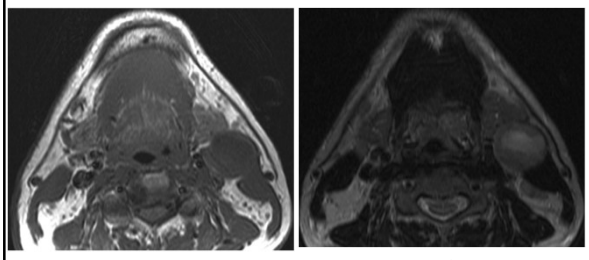
- Aggressive management:
  - Complete surgical resection
  - Radiotherapy and chemotherapy
- HPV-negative: dismal prognosis
- Active smokers and those with nodal metastases at presentation have worse prognosis
- Lymphatic and hematogenous spread:
  - Regional lymph nodes (50-70%)
  - Lung, bone, skin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

BSCC

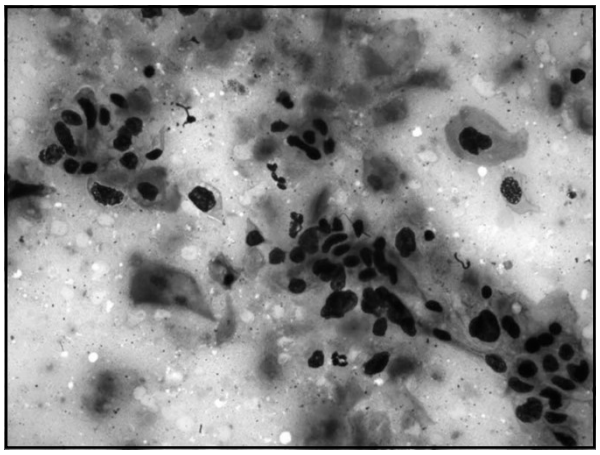
- HPV-positive:
  - Better overall prognosis than histologically similar non-HPV associated head and neck BSCC (Am J Surg Pathol 2008;32:1044-50)
- Any tumor appearing to arise in the larynx/hypopharynx but that involves the oropharynx should be tested for HPV (p16)
- p16 staining should be performed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

Viral-Associated Head and Neck Squamous Cell Carcinoma

MRI



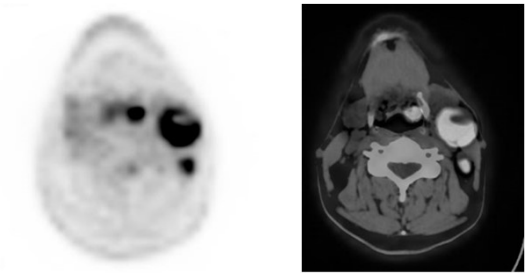
T1 T2



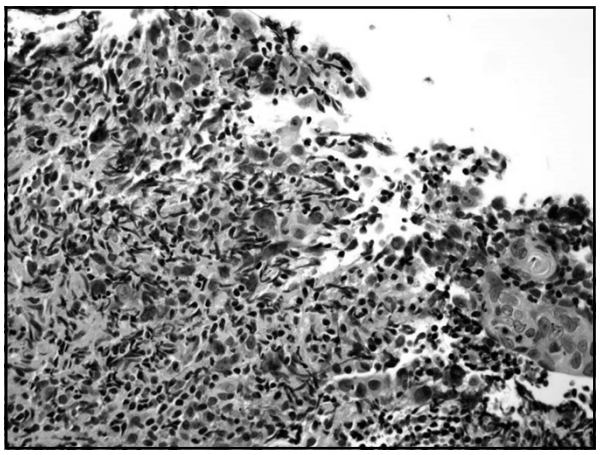
FNAB Diagnosis

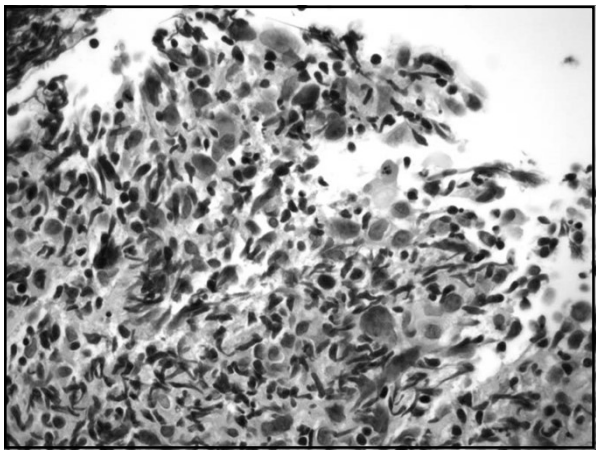
- **Metastatic poorly-differentiated carcinoma favor squamous cell carcinoma**

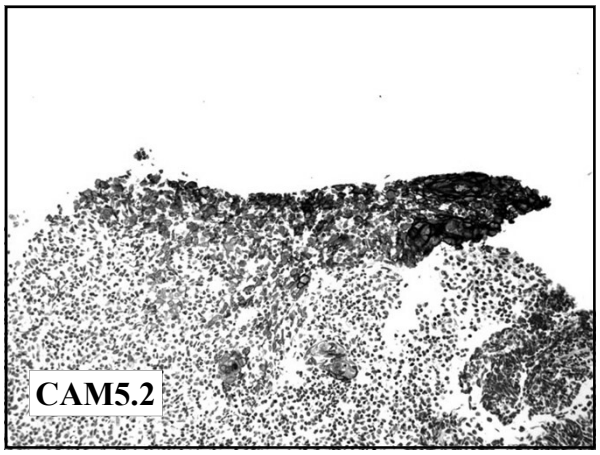
PET/CT



BOT Biopsy







Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers

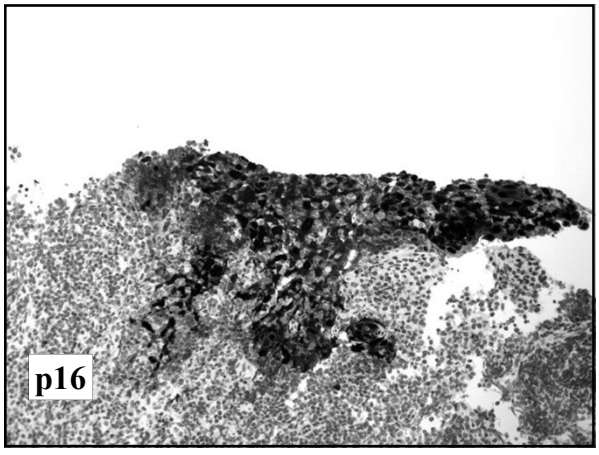
Maura L. Gillison, Wayne M. Koch, Randolph B. Capone, Michael Spafford, William H. Westra, Li Wu, Marianna L. Zahurak, Richard W. Daniel, Michael Viglione, David E. Symer, Keerti V. Shah, David Sidransky

J Natl Cancer Inst 2000;92:709-20

Basaloid Squamous Cell Carcinoma

HPV 16

- **p16 immunostaining and/or HPV DNA (ISH, PCR) correlates to the presence of HPV16**
- **Representing a reliable predictor of origin from the oropharynx**



Diagnosis

- **Oropharyngeal (Tonsillar) Carcinoma:**
  - **Poorly-differentiated squamous cell carcinoma**
  - **Squamous cell carcinoma with basaloid features**
  - **Nonkeratinizing carcinoma**

Nonkeratinizing Carcinoma

↓

Human Papillomavirus (HPV)

↓

Oropharyngeal Carcinoma

(HPV-associated SCC)

HPV-HNSCC

- **Incidence of HPV-related oropharyngeal HNSCC is rising:**
  - **increasing 11% over past 2 decades**
- **Incidence of HPV-unrelated HNSCC has stabilized**

Comparison between HPV-positive and HPV-negative SCC

	HPV positive SCC	HPV negative SCC
Age	Younger	Older
Gender	M = F	M > F
Race	Caucasian >>>> African American	Caucasian = African American
Risk factors (Tobacco/alcohol)	No known risk factors (usually nonsmokers, nondrinkers)	Associated with tobacco and/or alcohol use/abuse
Primary location	Oropharynx (base of tongue; tonsil)	All mucosal sites of the UADT
Histology	Nonkeratinizing carcinoma predominantly composed of basaloid cells	Keratinizing squamous cell carcinoma
p16	Positive	Negative
Prognosis	Better disease-free and overall survival	Worse disease-free and overall survival
Tumor Stage at presentation	Often higher (more nodal metastasis)	Often lower

Metastatic Cervical Carcinoma with an Unknown Primary Tumor (MCCUP)

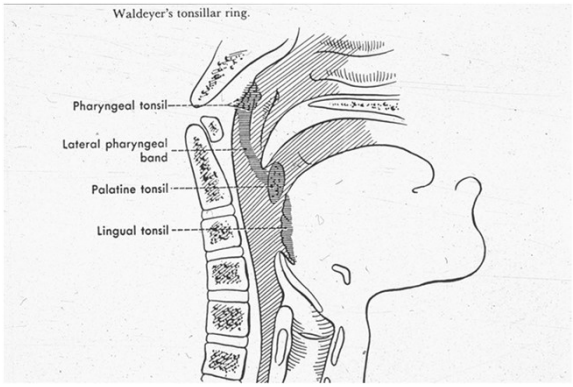
- **Definition:**
  - **Overt neck mass harboring a cytologically or histologically proven metastatic carcinoma in the absence of signs and symptoms of a primary neoplasm or of a clinically detectable mass:**
    - **no history of previous malignancy or cancer ablation of any indeterminate lesion**
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

Histology of Metastases from Unknown Primary Tumors

	Location		
Histology	Cervical	Supraclavicular	Total
Squamous carcinoma	153	30	183
Adenocarcinoma	6	54	60
Undifferentiated carcinoma	44	25	69
Thyroid carcinoma	6	5	11
Melanoma	7	0	7
Sarcoma	2	2	4
Salivary gland carcinoma	2	0	2

Location of Primary Head and Neck Carcinomas Originally Considered Occult

Location	Total numbers
Nasopharynx and oropharynx	31
Tonsil/base of tongue	31
Thyroid	21
Hypopharynx	19
Supraglottis	12
Oral cavity	8
Nose and sinuses	4
Esophagus	3
Miscellaneous head and neck	11
Total	140



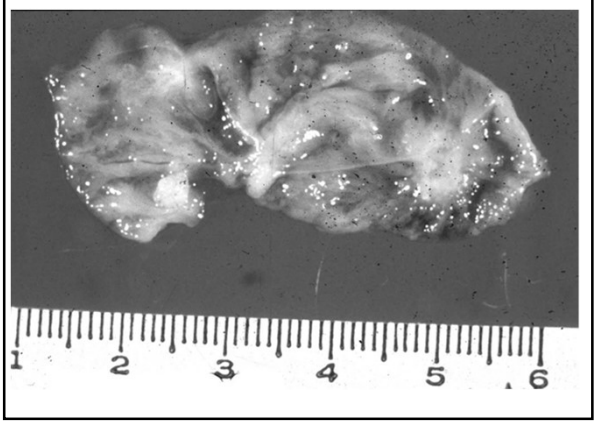
Discovery of Primary Tumor Following Definitive Therapy

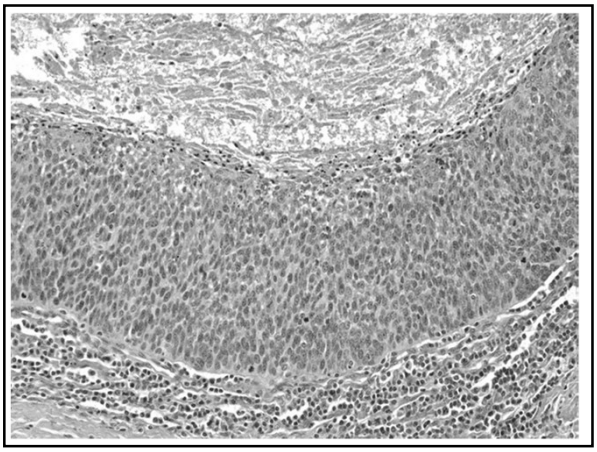
Author (Ref.)	Total no. cases	Primary detected (% of total)	Primary found (%) Above clavicle	Primary found (%) Below clavicle
Smith et al. (40)	53	15 (28.3)	47	53
Jesse and Neff (12)	127	48 (37.8)	60	40
Jesse et al. (13)	210	37 (17.6)	75	25
Comess et al. (4)	103	42 (40.8)	78	22
France and Lucas (41)	43	12 (27.9)	66	34
Marchetta et al. (42)	33	15 (45.4)	53	47
Acquarelli et al. (43)	31	12 (38.7)	50	50
Total	600	181 (30.0)	61 (average)	39 (average)

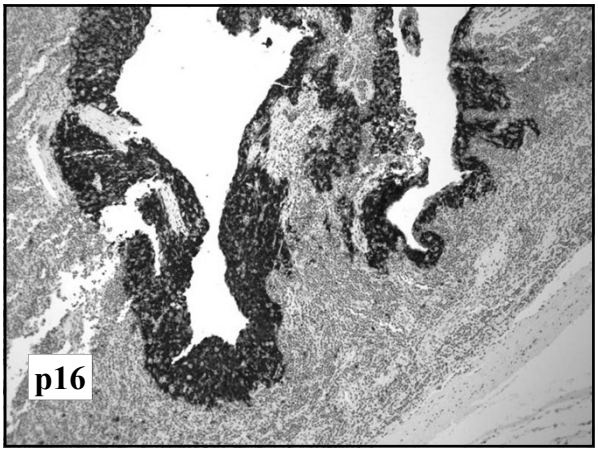
Branchiogenic Carcinoma Criteria*

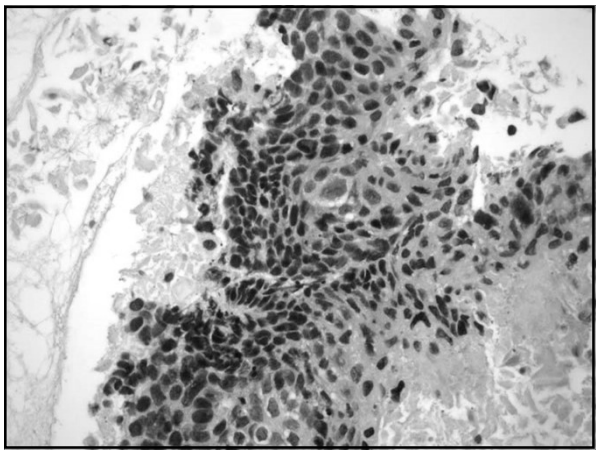
- **Cervical tumor occurs along line extending from anterior to the tragus along the anterior border of the SCM to the clavicle**
- **Histology c/w origin from tissue known to be present in branchial vestige**
- **No primary source for carcinoma on at least 5-year f/u**
- **Histologic evidence of carcinoma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

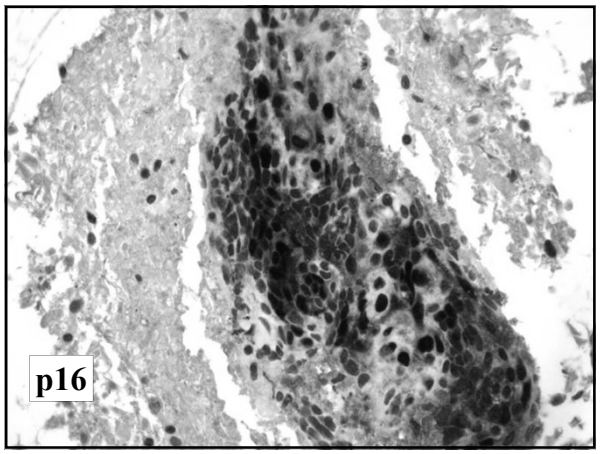
***Martin et al. Ann Surg 1950;132:825-832**







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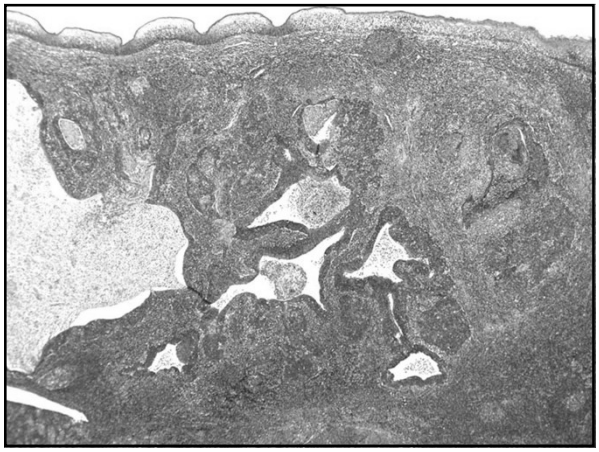

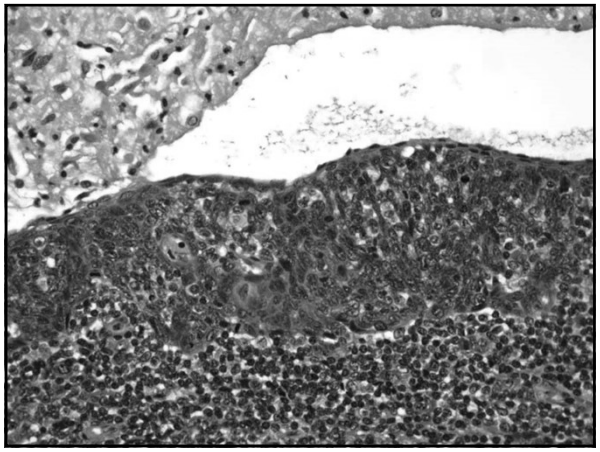

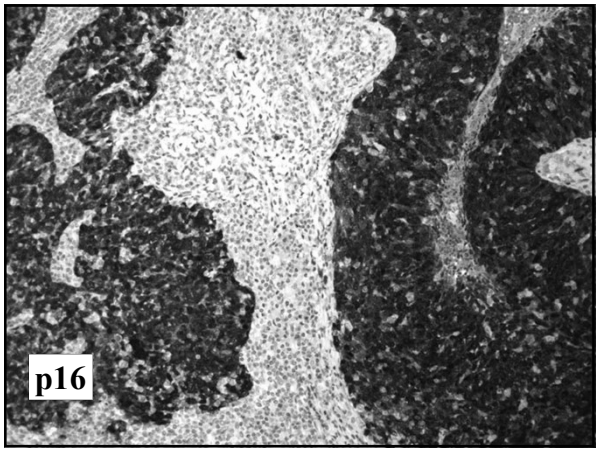
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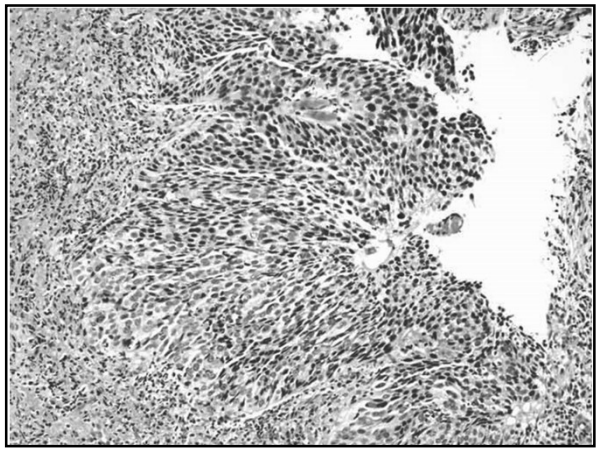
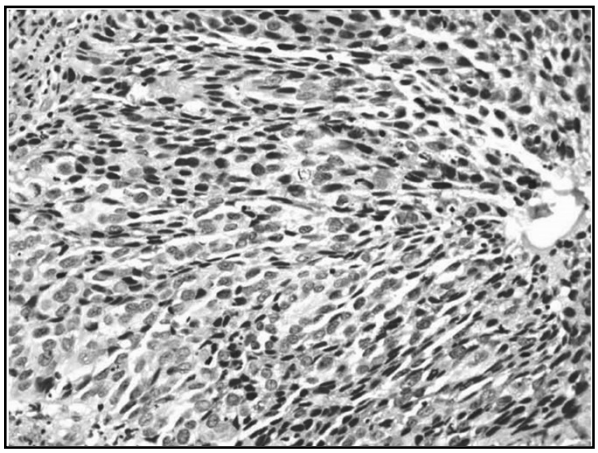
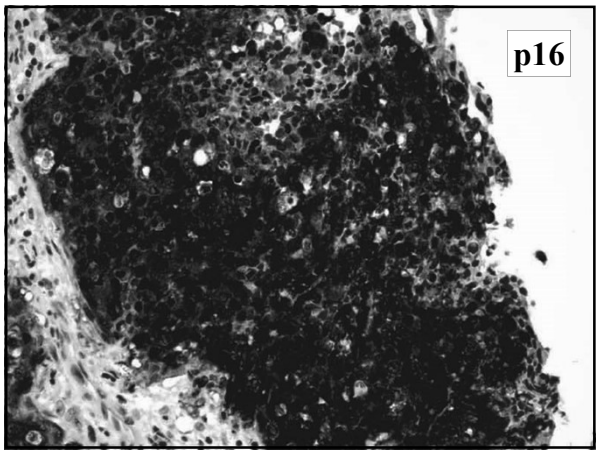
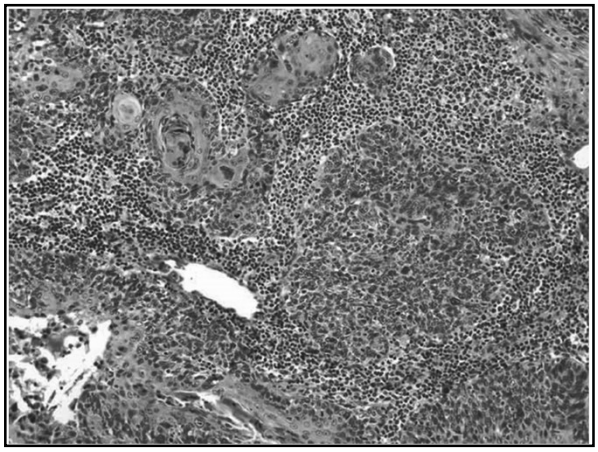
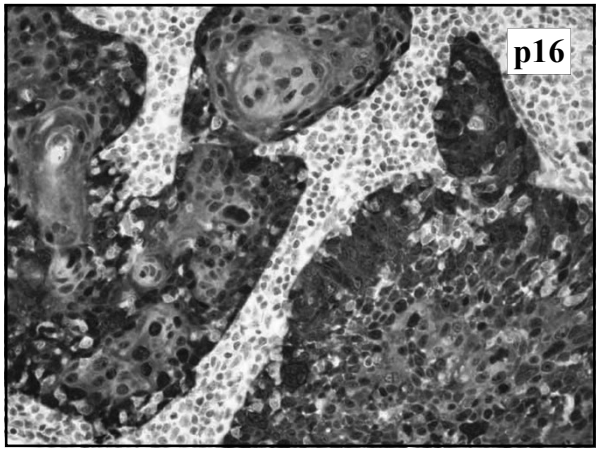
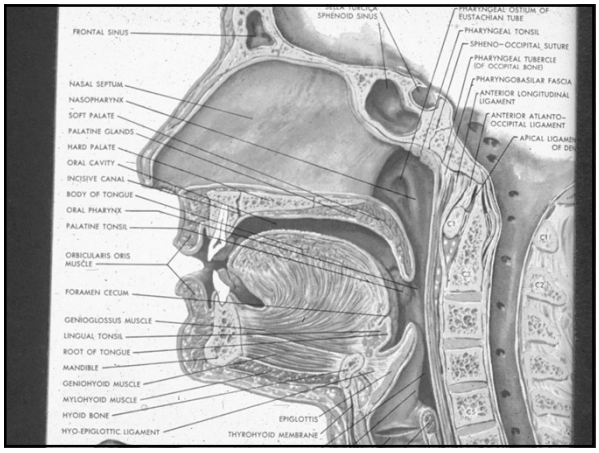












Nasopharyngeal Carcinoma (NPC)
WHO Classification

- **Type I = Keratinizing:**
  - **well-, moderately, poorly-differentiated**
- **Type II = Nonkeratinizing:**
  - **Differentiated type (Transitional Cell or Cylindrical Cell Carcinoma)**
  - **Undifferentiated type (Lymphoepithelioma)**

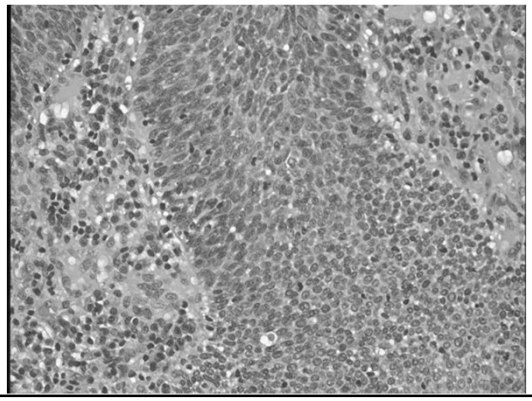
Nasopharyngeal Carcinoma Clinical Features

- In USA: < 0.25% of all cancers
- In China: 10% of all cancers
- M > F; primarily occurs in older age groups (> 6th decade) but may occur in pediatric ages
- Most commonly occurs along lateral wall
- Symptoms: neck mass, aural-related, nasal obstruction, epistaxis, pain, headache, cranial nerve deficit(s)

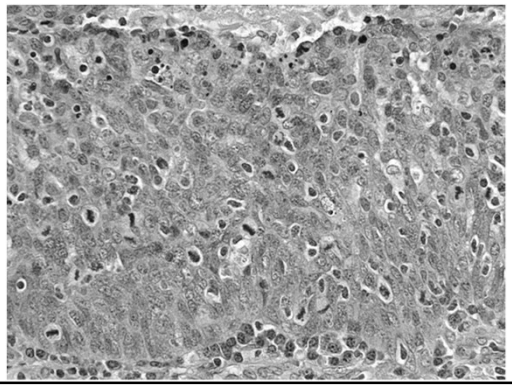
Nasopharyngeal Carcinoma Etiologic Factors

- Genetic and geographic
- Epstein-Barr virus (EBV):
  - Elevated IgG and IgA antibodies
  - ISH and PCR detection of EBV genomes
  - May be an early initiating event in the development of NPC
- Diet, poor hygiene, environmental

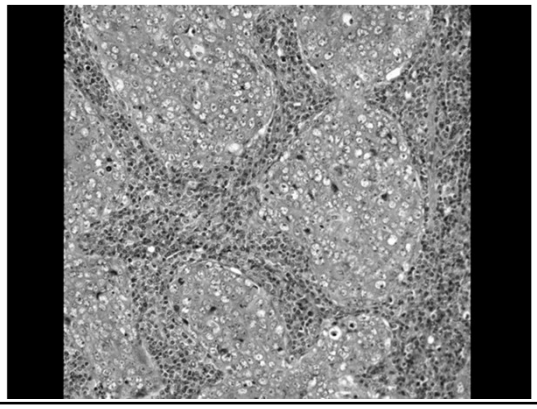
NPC, nonkeratinizing differentiated



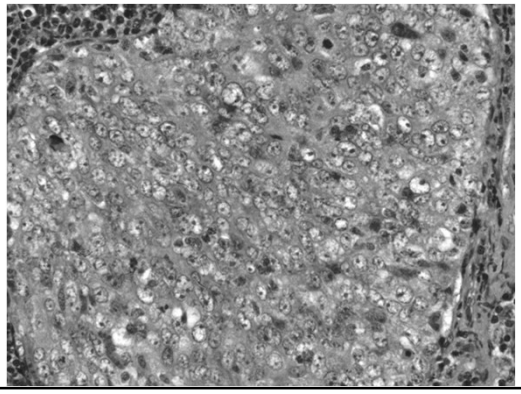
NPC, nonkeratinizing differentiated



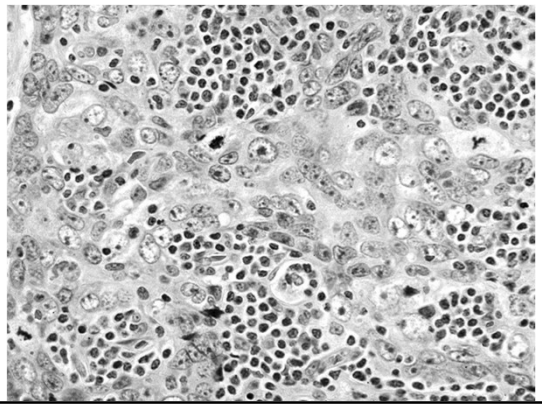
NPC, nonkeratinizing undifferentiated



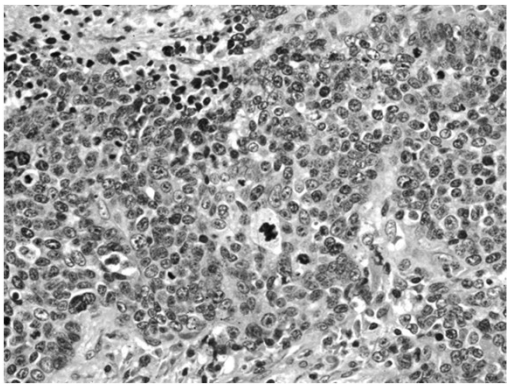
NPC, nonkeratinizing undifferentiated

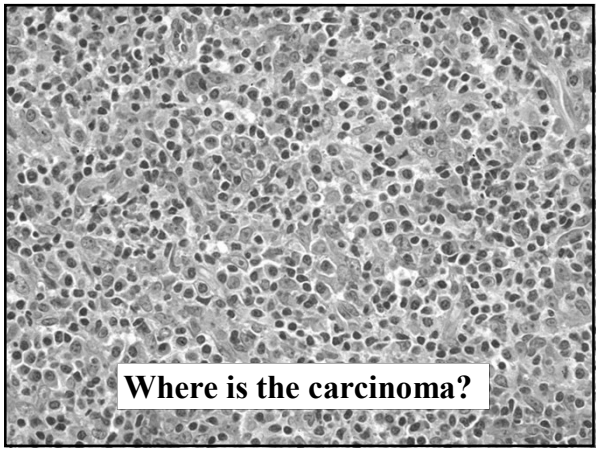


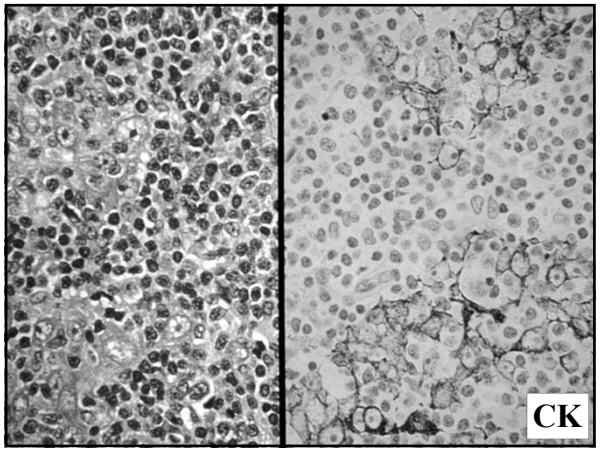
NPC, nonkeratinizing undifferentiated

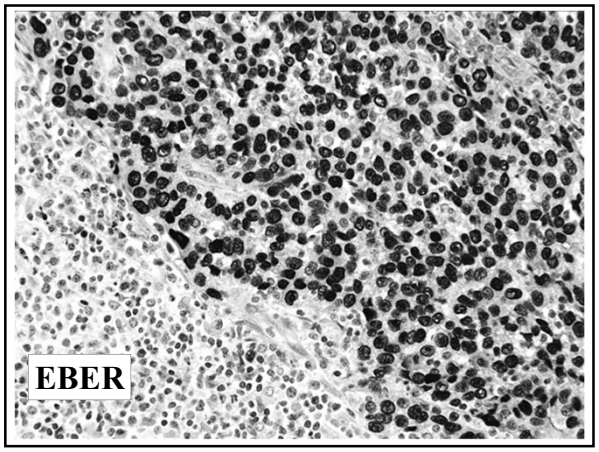


NPC, nonkeratinizing type, mixed







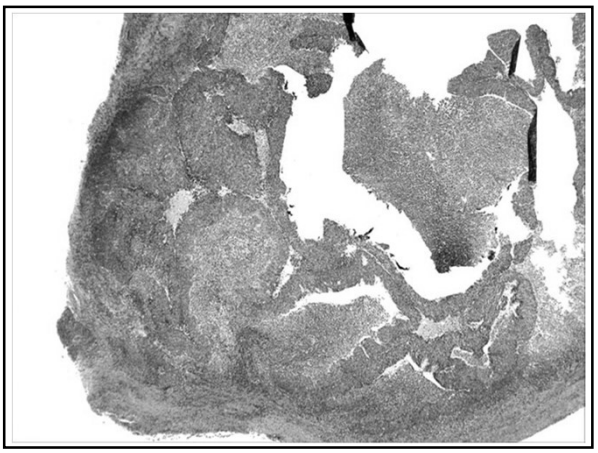


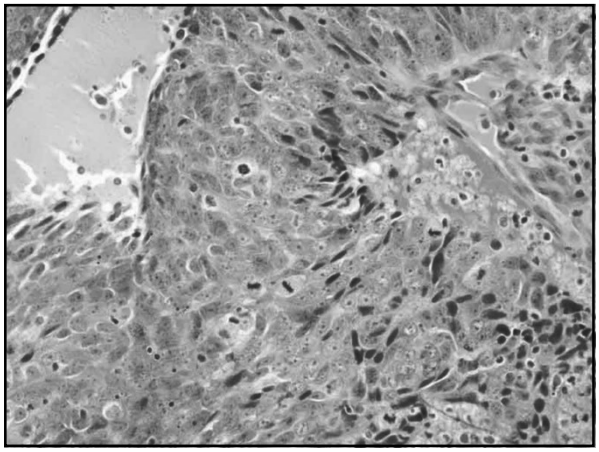
Nasopharyngeal Carcinoma (NPC)

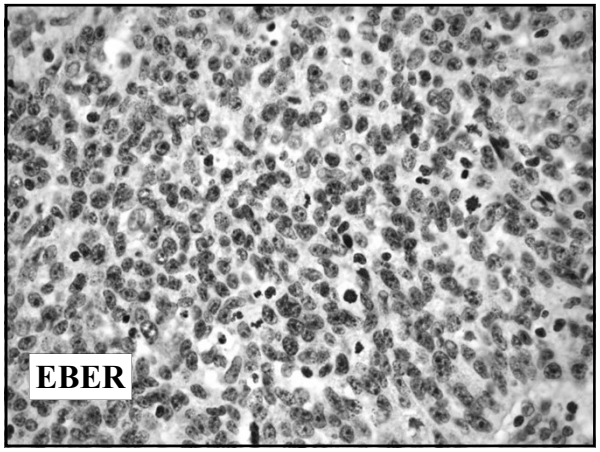
	Keratinizing	Nonkeratinizing Differentiated	Nonkeratinizing Undifferentiated
Percent	Approximately 25%	Least common - < 15%	Most common > 60%
Sex/Age	M > F; 4th- 6th decades	M > F; 4th - 6th decades	M > F; 4th - 6th decades; may occur in children
EBV	Weak association	Strong association	Strong association
XRT Response	Radio-responsiveness is not good	Radioresponsive	Radioresponsive
5-Yr survival	20-40%	65%	65%

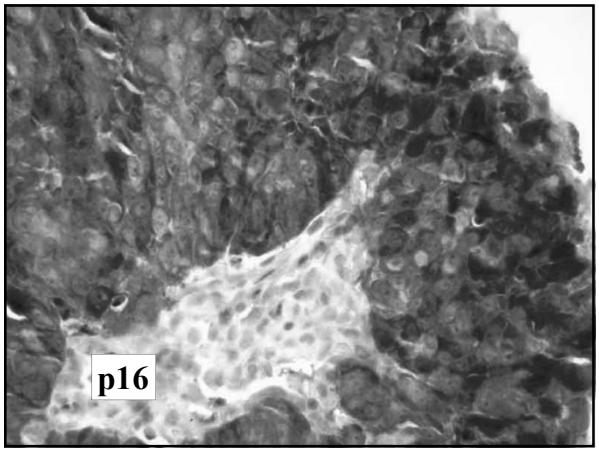
Nasopharyngeal Carcinoma Differential Diagnosis

- **Non-Hodgkin lymphoma**
- **Mucosal malignant melanoma**
- **Mesenchymal (e.g., rhabdomyosarcoma)**









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 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
- Select variants of squamous cell carcinoma:
  - Clinical and pathologic features

Squamous Cell Lesions Conclusions

- Viral carcinogenesis causally associated with HNSCC
- Strategy incorporates p16 IHC, HPV ISH and PCR, as well as EBER
- Classification:
  - HPV-associated SCC
  - EBV-associated SCC
- Overall better prognosis than non-viral associated HNSCC