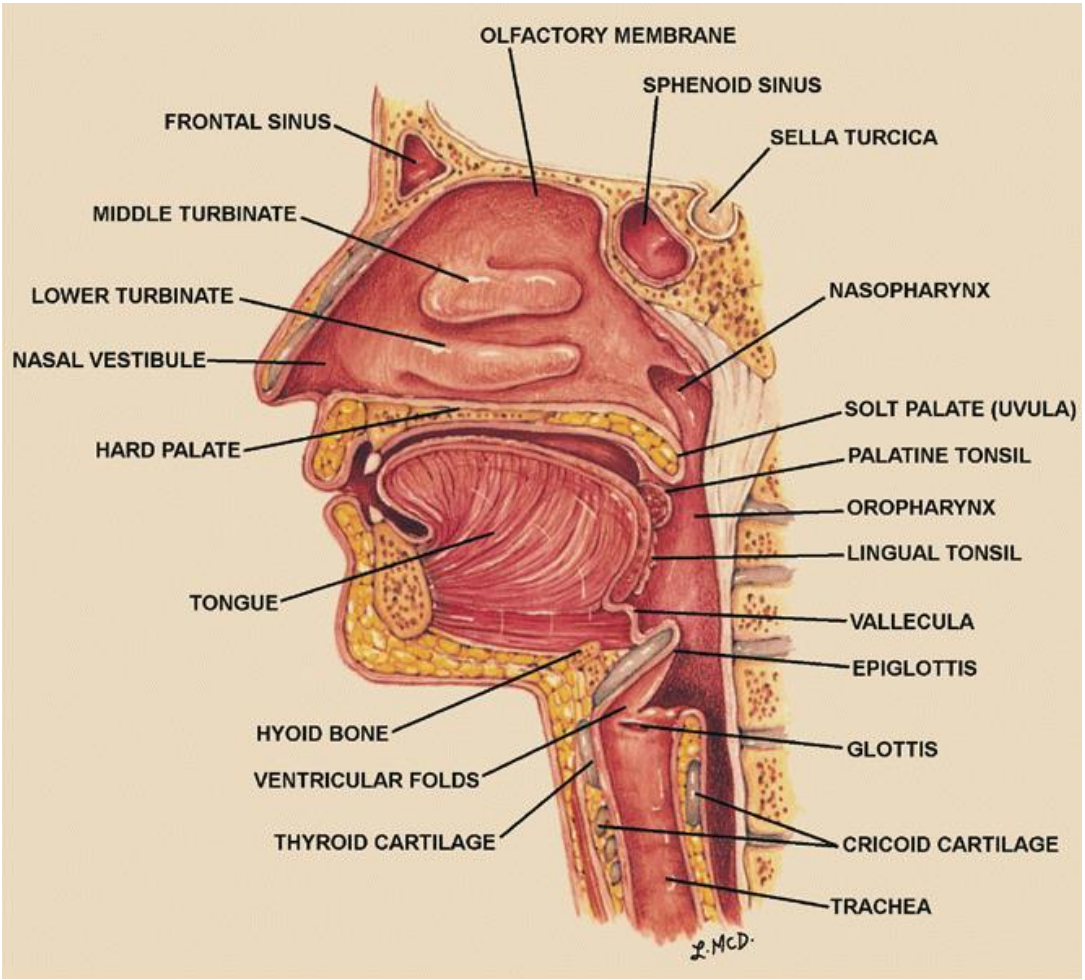
HEAD AND NECK CANCER

Kenneth Alonso, MD, FACP

Anatomy

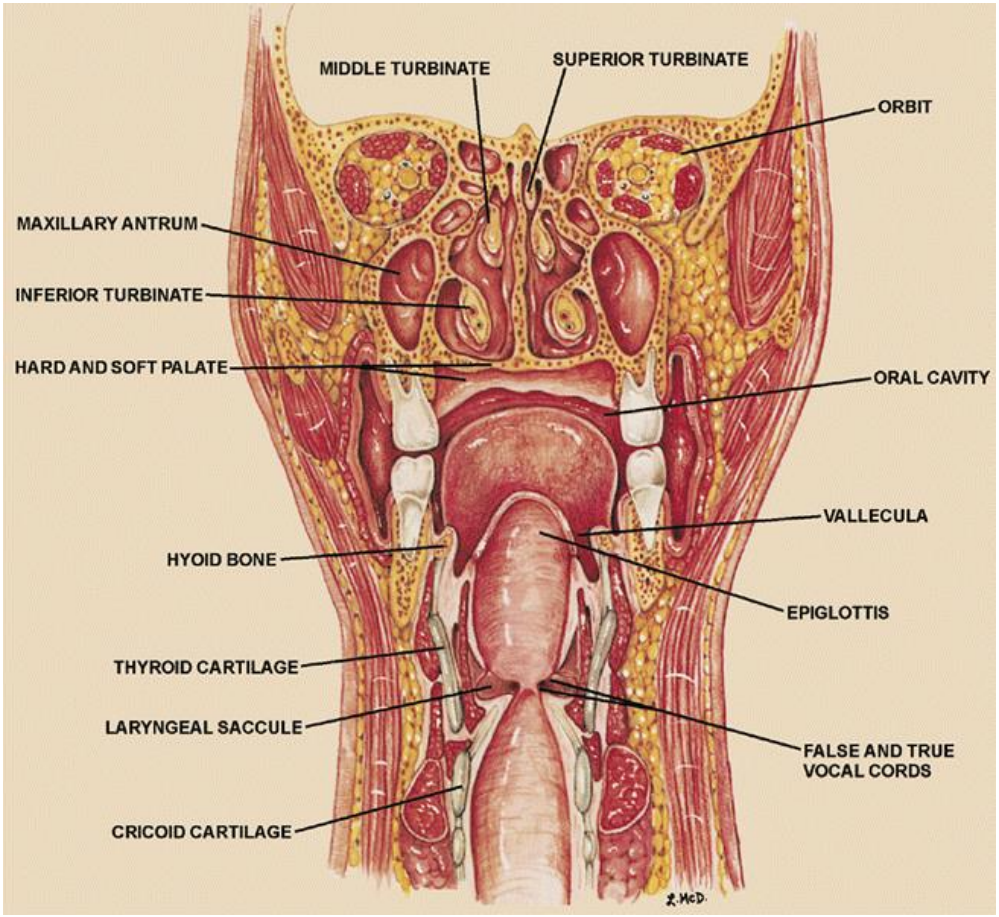


A sagittal section through the head at the level of the molar teeth displays the anatomy of the nasal cavity, as well as the pharynx, larynx, and some of the paranasal sinuses.

Fig. 1-1

Mills, SE, Gaffey, MJ, Frierson ,HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Anatomy



A coronal section through the head at the level of the molar teeth displays the anatomy of the nasal cavity, as well as the pharynx, larynx, and some of the paranasal sinuses.

Fig. 1-2

Mills, SE, Gaffey, MJ, Frierson ,HF. , "Tumors of the upper aerodigestive tract and ear." Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Anatomic limits

- The oral cavity extends from the skin-vermilion junctions of the anterior lips to the junction of the hard and soft palates above and to the line of circumvallate papillae below and is divided into the following specific areas:
- Lip.
- Anterior two thirds of tongue.
- Buccal mucosa.
- Floor of mouth.
- Lower gingiva.
- Retromolar trigone.
- Upper gingiva.
- Hard palate.

Anatomic limits

- The oropharynx is divided into the following parts:
- Base of the tongue, which includes the pharyngoepiglottic folds and the glosso-epiglottic folds.
- Vallecula.
- Tonsillar region, which includes the fossa and the anterior and posterior pillars.
- Soft palate, which includes the uvula.
- Posterior and lateral pharyngeal walls.

Anatomic limits

- The hypopharynx extends from the plane of the hyoid bone above to the plane of the inferior border of the cricoid cartilage below.
- The hypopharynx is composed of:
- The pyriform sinus.
- The postcricoid area.
- The posterior pharyngeal wall.
- It does not include the larynx

Anatomic limits

- The larynx is divided into the following three anatomical regions:
- The supraglottic larynx includes the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids.
- The glottis includes the true vocal cords and the anterior and posterior commissures.
- The subglottic region begins about 1 cm below the true vocal cords and extends to the lower border of the cricoid cartilage or the first tracheal ring.

NASOPHARYNX

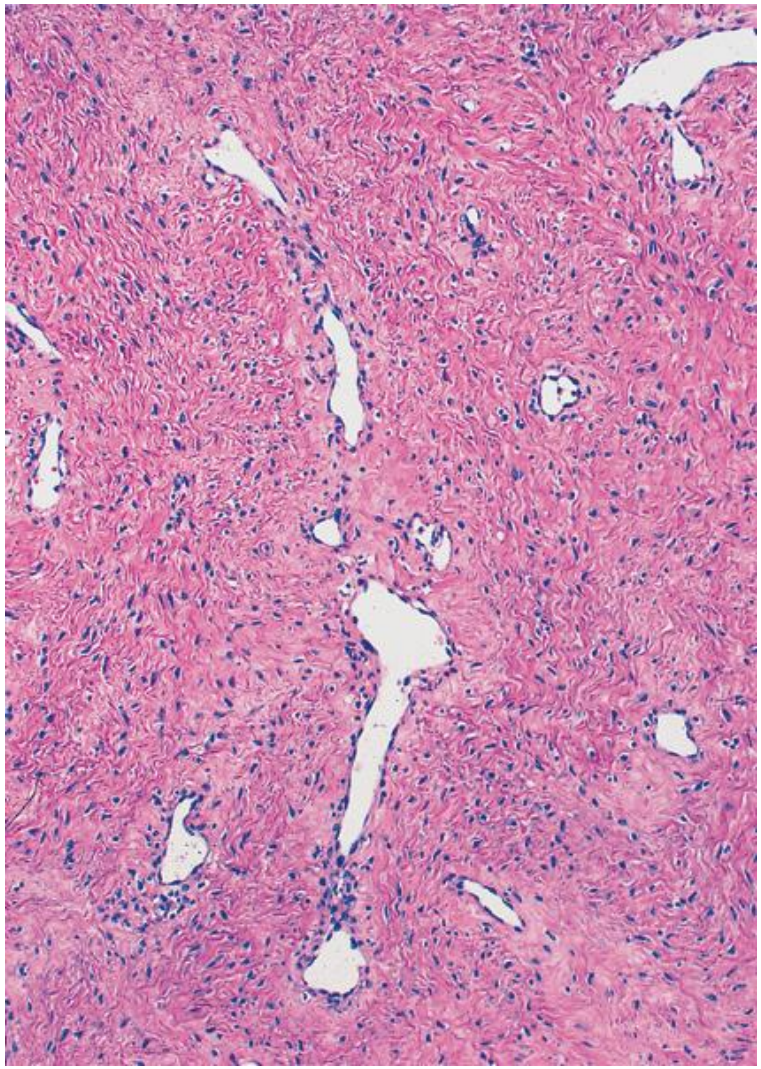
Nasopharyngeal angiofibroma

- Nasal polyps are usually a response to chronic allergen exposure.
- Angiofibromas are fibrovascular polyps generally found in pre-adolescent males.
- Fair skin, red headed
- There is proliferation of fibrovascular stroma of the posterolateral wall of the roof of the nasal cavity
- Bleed.
- Regress at puberty.

Nasopharyngeal angiofibroma

- Microscopic examination:
- There is edematous fibrovascular tissue.
- A heavy eosinophilic infiltrate noted in submucosal tissues.
- Locally aggressive
- 20% recur following surgery
- 9% mortality (hemorrhage, intracranial extension)
- Associated with familial adenomatous polyposis

Angiofibroma



This angiofibroma is composed of both very small vascular spaces as well as scattered larger vascular channels. The characteristic, haphazardly arranged stromal collagen is seen.

Fig. 9-17

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

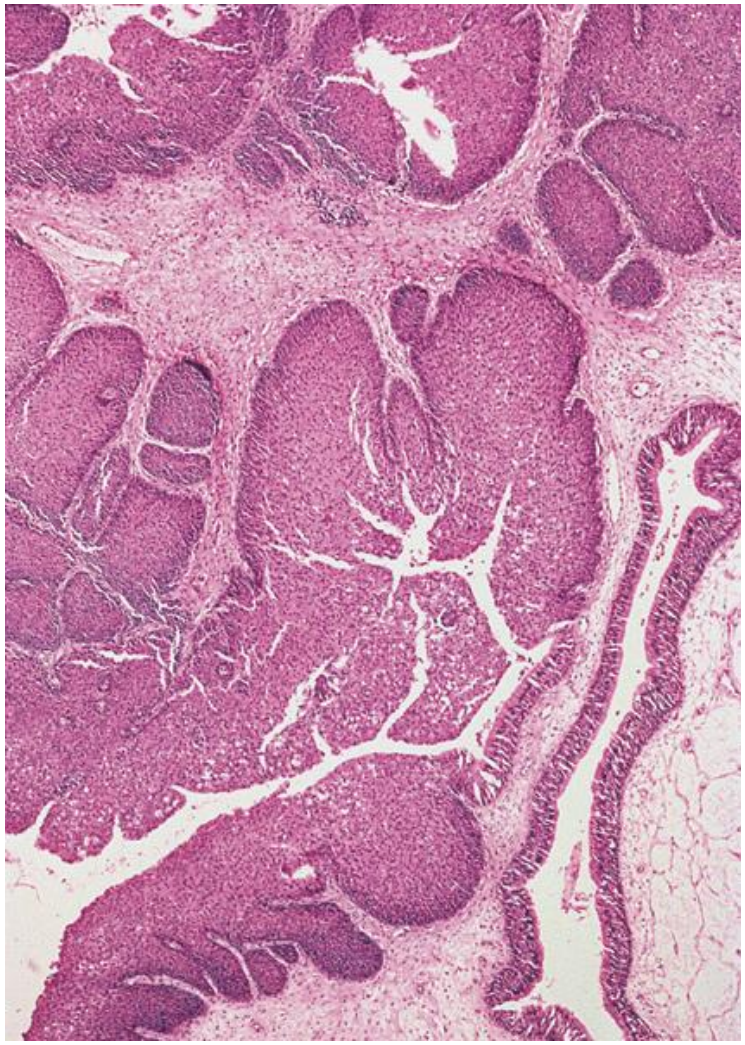
Sinonasal papilloma

- Men
- 30-60 years of age
- Arises from Schneiderian (respiratory) mucosa lining the nasal cavity and paranasal sinuses
- Exophytic presentation most common
- Cylindrical type also seen (but not HPV related)
- Endophytic (inverted)
- Locally aggressive (to orbit or to cranial vault)
- Recur if not adequately excised
- 10% progress to cancer

Inverted papilloma (nasopharynx)

- HPV types 6 and 11 associated with exophytic and endophytic presentations
- If not adequately excised, it has a high rate of recurrence, with the potentially serious complication of invasion of the orbit or cranial vault; rarely, frank carcinoma may also develop.

Inverted papilloma

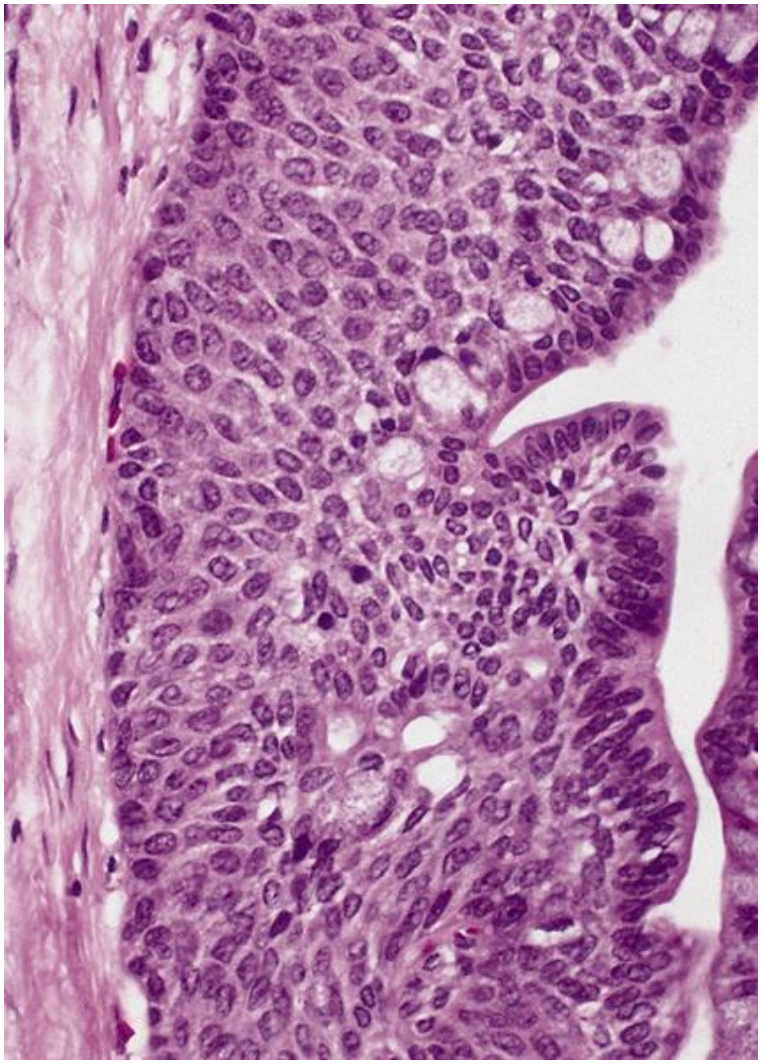


Most inverted Schneiderian papillomas arise from the lateral nasal wall and are composed of epithelial- lined, duct-like structures that endophytically project into the underlying stroma.

Fig. 3-4

Mills, SE, Gaffey, MJ, Frierson ,HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Inverted papilloma

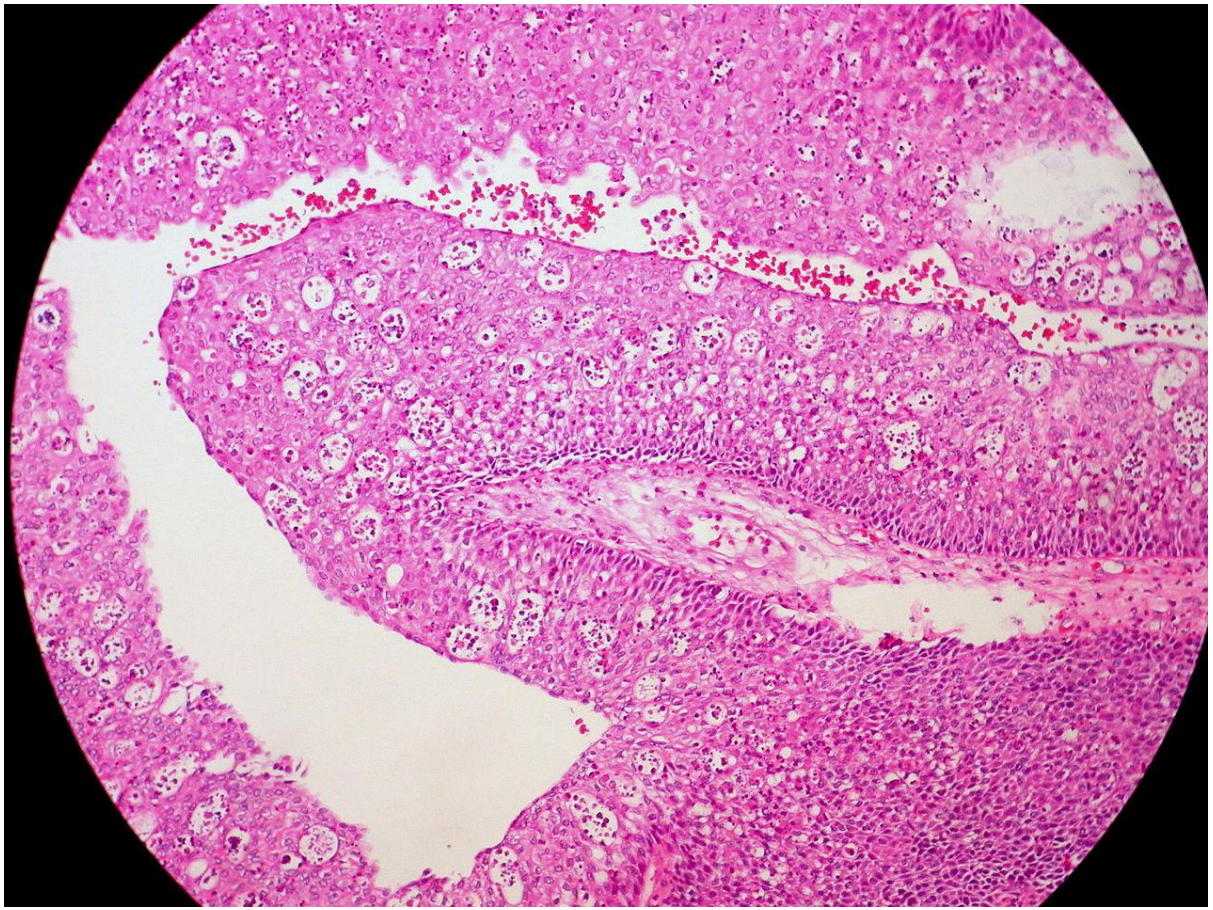


Most of the epithelial cells are basaloid squamous cells, but the luminal surface in this section is lined by columnar duct-type epithelial cells that overlie the epidermoid cells. Several pale-staining cells within the epithelium are mucocytes

Fig. 4-129

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Endophytic (inverted) papilloma

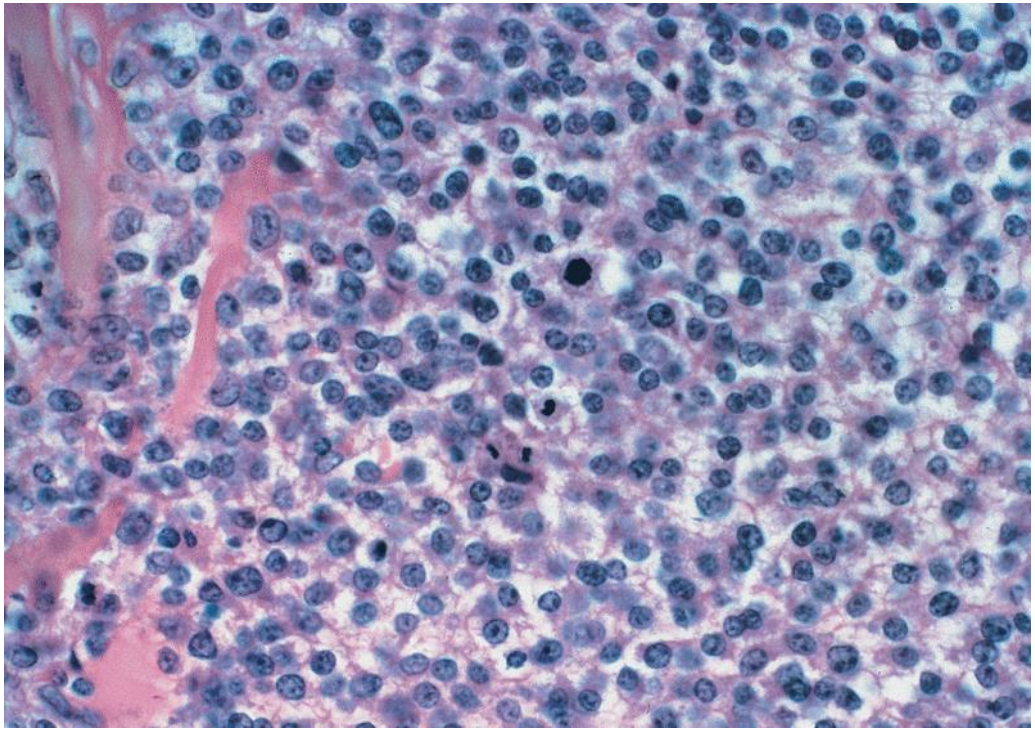


Multiple microabscesses present.

Olfactory neuroblastoma (esthesioneuroblastoma)

- Bimodal age distribution:
- Peaks at 15 and 50 years of age
- Present with nasal obstruction or with epistaxis
- Arise from neuroectodermal olfactory cells present within the mucosa
- Superior aspect of nasal cavity
- Nests of small rounded cells separated by a fibrovascular stroma.
- Surgery, chemoradiation depending upon disease stage
- Survival rate at 5 years is 90% in early stage tumors; 40% if advanced

Primitive neuroectodermal tumor

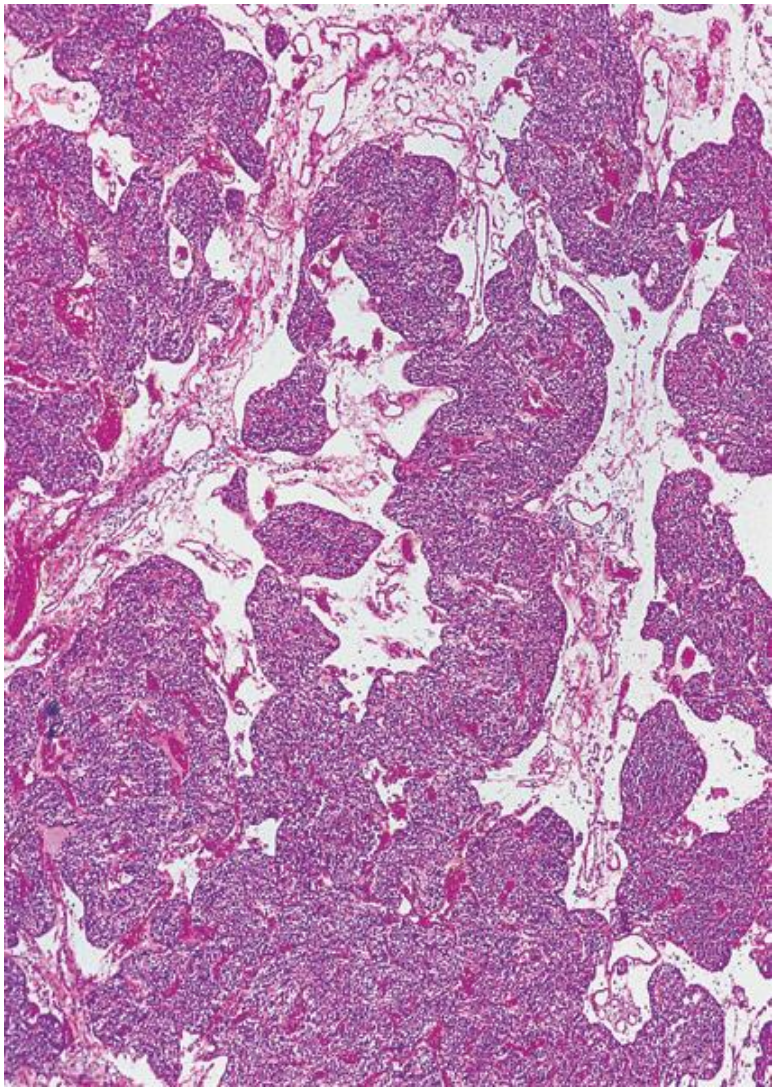


The neoplastic cells are small, and often appear to be composed almost entirely of a vesicular or hyperchromatic nucleus with inconspicuous nucleoli. Mitotic figures are easily identified.

Fig. 7-100

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Olfactory neuroblastoma



Olfactory neuroblastomas grow as sharply demarcated nests of cells in an edematous stroma. Olfactory neuroblastomas may also grow as diffuse sheets of cells in a highly vascular stroma.

Fig. 7-53

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Extra-nodal NK and T-cell disease

- Most commonly presenting as a destructive midline mass involving the nasopharynx
- Once known as Lethal midline granuloma, Malignant midline reticulosis, angiocentric T-cell lymphoma
- 5-10% of non-Hodgkin lymphomas in China
- Increasing incidence in Latin America.
- Rare in the US and Europe
- Males twice as likely as females to have disease
- Rapidly progressive, necrotizing midfacial process affecting the nasal, nasopharyngeal, sinonasal, palatal, and oropharyngeal structures.

Extra-nodal NK and T-cell disease

- 15-35% present extra-nasally
- May mimic polyangiitis with granulomatosis clinically
- If in skin, females twice as likely as males to have disease
- Microscopically:
- Diffuse polymorphic and atypical lymphoid infiltrate.
- Angiocentric and angiodestructive growth patterns with associated necrosis.
- Peripheral hyaline necrosis of blood vessels as a histologic hallmark.

Extra-nodal NK and T-cell disease

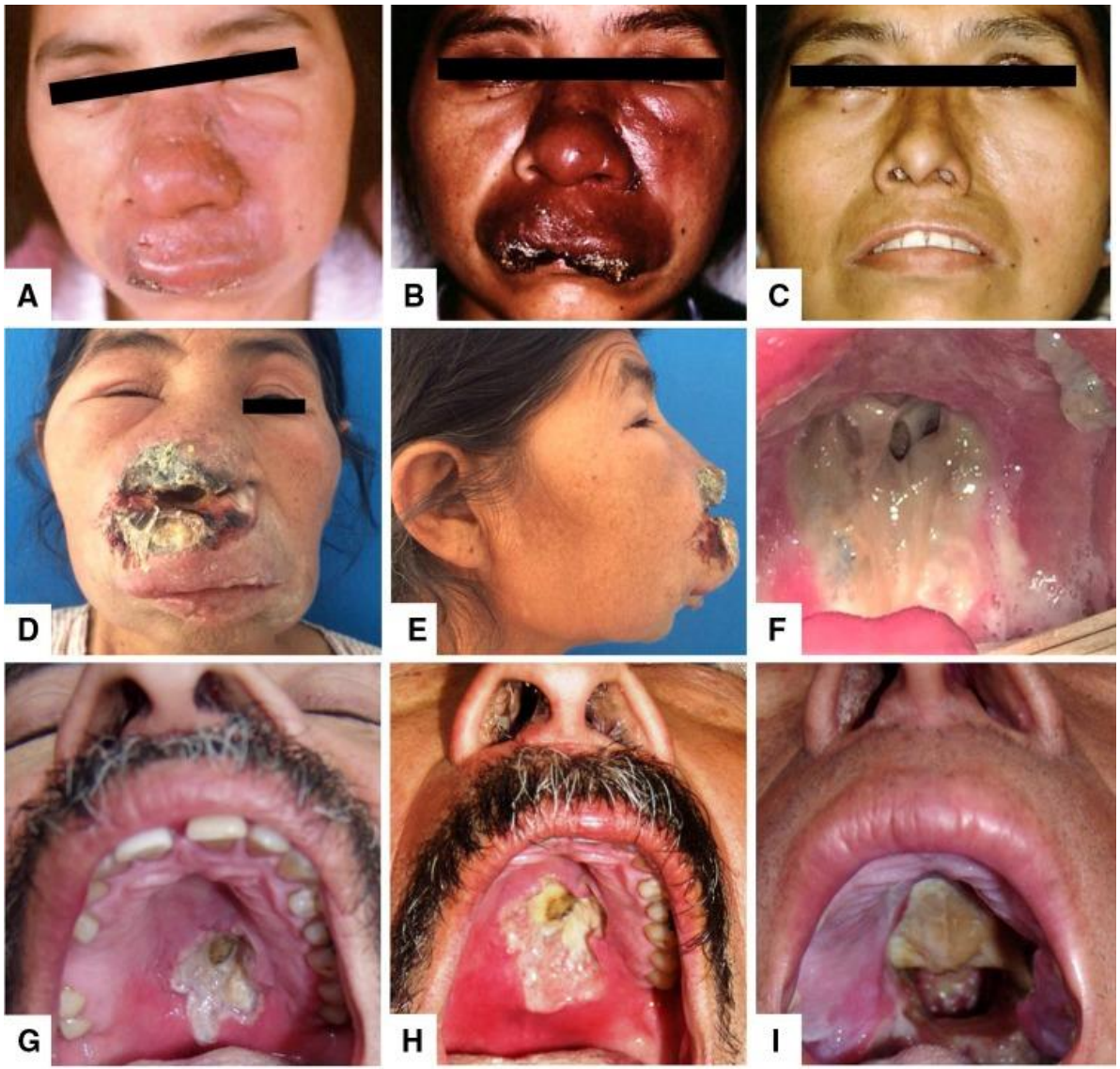
- EBV present in all cases
- Clonal episomal form present prior to clonal expansion
- EBER positive (latency type I)
- LMP positive (latency type II)
- Frequent 30 base pair deletion in LMP1 gene
- Decreased immune recognition
- Lymphogenesis
- Infected NK cells secrete IL-9 and IL-10, promoting cell activation and proliferation

Extra-nodal NK and T-cell disease

- CT and MRI to evaluate local invasion
- PET/CT to identify extra-nasal lesions
- Immuno-silenced microenvironment is related to aggressive behavior and advanced clinical stage
- Low expression of FOXP3 / PDL1 and high expression of CD68
- Age over 60, extra-nasal presentation, B symptoms are poor risk factors
- Elevated β-2 microglobulin, soluble IL-2, free EBV DNA are markers of poor risk

Extra-nodal NK and T-cell disease

- SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, etoposide) as frontline therapy in fit patients
- Radiation therapy following L-asparaginase based chemotherapy
- 40-60% 5 year survival



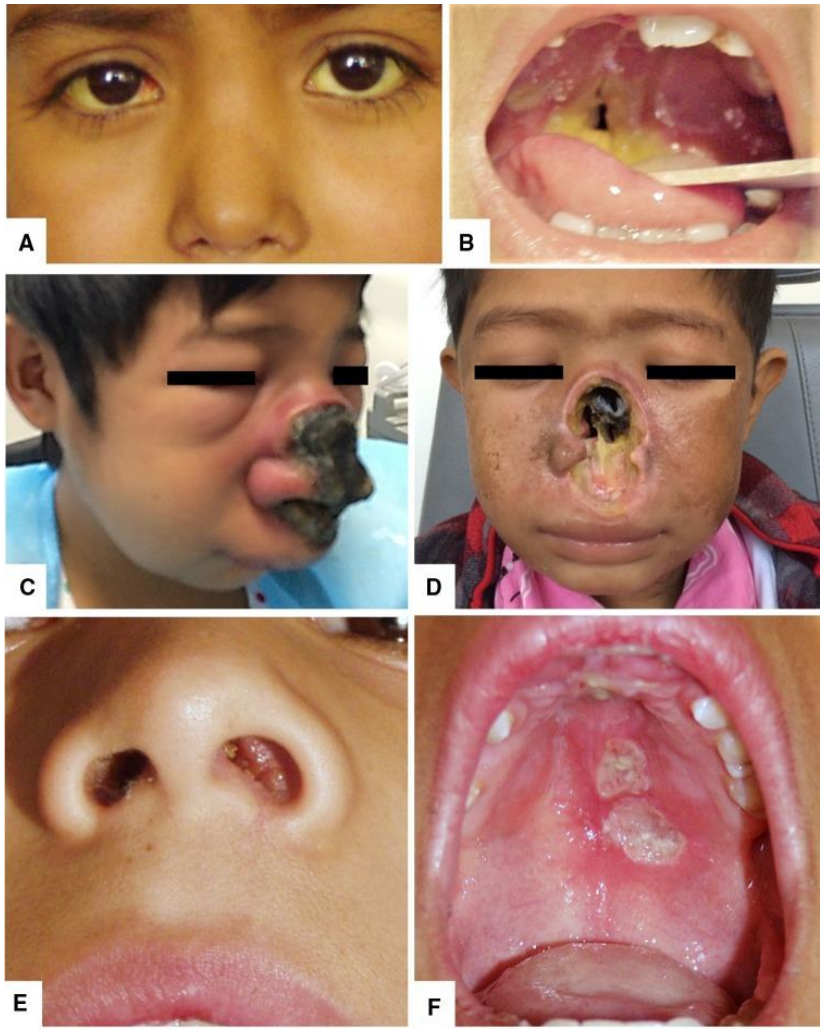
Clinical features of extra-nodal NK and T cell disease

A-B 27 year old woman with progression over 10 days.
C Following 7 years of concurrent chemotherapy

D-F 60 year old woman who died over a course of 2 months

G-I 54 year old man who died over a course of 2 weeks

Sanchez-Romero, C, Paes de Almeida, O, Rendon Henao, J, Carlos, R, "Extra-nodal NK/T-Cell Lymphoma, Nasal Type in Guatemala", Head and Neck Pathology 2019 Dec;13(4):624-634. doi: 10.1007/s12105-019-01027-z. Figure 1 Accessed 04/20/2021



Clinical features of extra-nodal NK and T cell disease

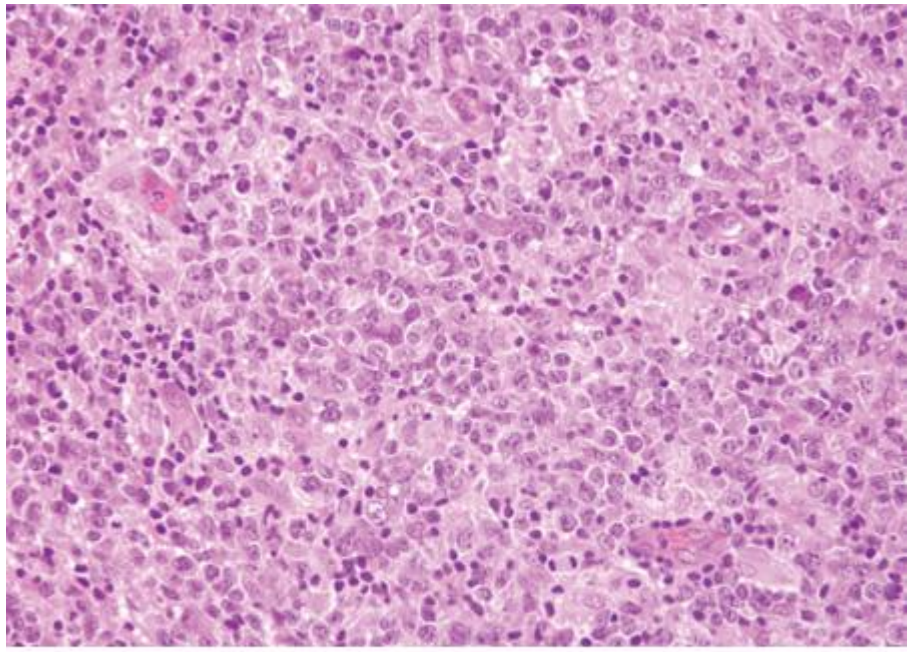
A-B 8 year old girl with hemophagocytic syndrome. Died.

C-D 14 year old boy with severe disfigurement although in remission

E-F 11year old boy now in remission following therapy. <u>The common clinical presentation in pediatric cases.</u>

Sanchez-Romero, C, Paes de Almeida, O, Rendon Henao, J, Carlos, R, “Extra-nodal NK/T-Cell Lymphoma, Nasal Type in Guatemala”, Head and Neck Pathology 2019 Dec;13(4):624-634. doi: 10.1007/s12105-019-01027-z. Figure 2 Accessed 04/20/2021

Extranodal T-cell lymphoma



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

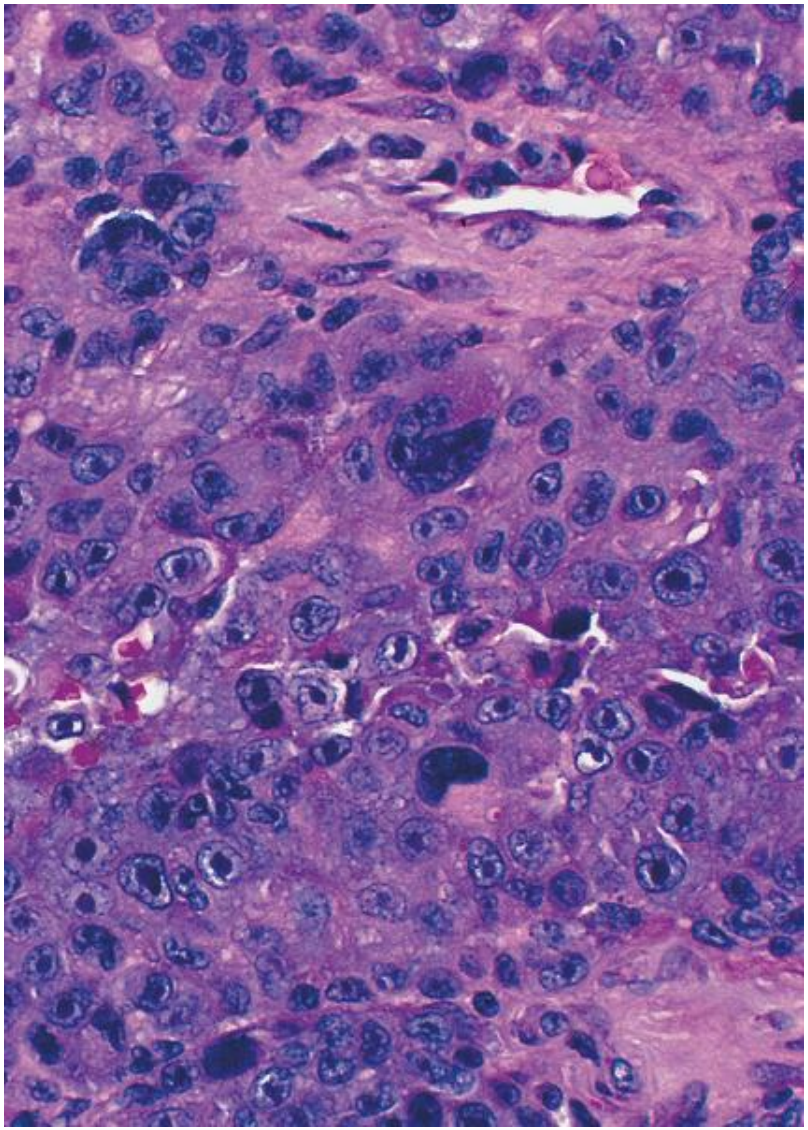
Neoplastic cells are both small and large.
Angiocentric.

Fig. 6-10 Accessed 04/27/2010

Malignant melanoma

- More common in Africans, Native Americans, and Japanese
- Mean age at diagnosis is 65-70 years
- Characterized by vascular invasion, polymorphous tumor cell population and necrosis
- Surgical resection is often followed by adjuvant radiotherapy
- 50% recur
- <40% 5 year survival

Malignant melanoma



Marked nuclear pleomorphism noted. Other patterns include small cell, epithelioid,and fibroid types.

Fig. 7-95

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Nasopharyngeal carcinoma

- Most frequent childhood cancer in North Africa
- Common in adults in China as well as in Southeast Asia
- Rare in the US
- Present with unilateral nasal obstruction, epistaxis
- Occult primary
- 60% positive nodes (level I).
- 80% positive nodes (levels I-II)
- Trismus, diplopia, epiphora, anosmia, dental pain, depending upon site of invasion.

Nasopharyngeal carcinoma

- WHO I locally aggressive
- Locally recur after excision.
- WHO II, III metastasize to other organs.
- Survival 60% all stages
- If T_4, survival, 30%.
- The pretreatment plasma EBV DNA level is identified as a significant, negative prognostic factor for progression-free survival and overall

Nasopharyngeal carcinoma

- Keratinizing variant
- Non-keratinizing variant associated with EBV
- Undifferentiated/basaloid variant comprised of large epithelial cells with vesicular nuclei, prominent nucleoli, disposed in syncytium-like array.
- Lymphovascular invasion
- 80% smokers
- SMARCB1 deficient variant may present as sheets of plasmacytoid or rhabdoid cells (40%) or as basaloid cells (60%)
- Always pancytokeratin positive

Nasopharyngeal carcinoma

- Usually treated with radiotherapy
- 70+% 5-year survival for keratinizing and non-keratinizing variant
- 20% 5-year survival for undifferentiated variants
- Gemcitabine and paclitaxel for recurrent or metastatic nasopharyngeal cancer

NUT midline carcinoma

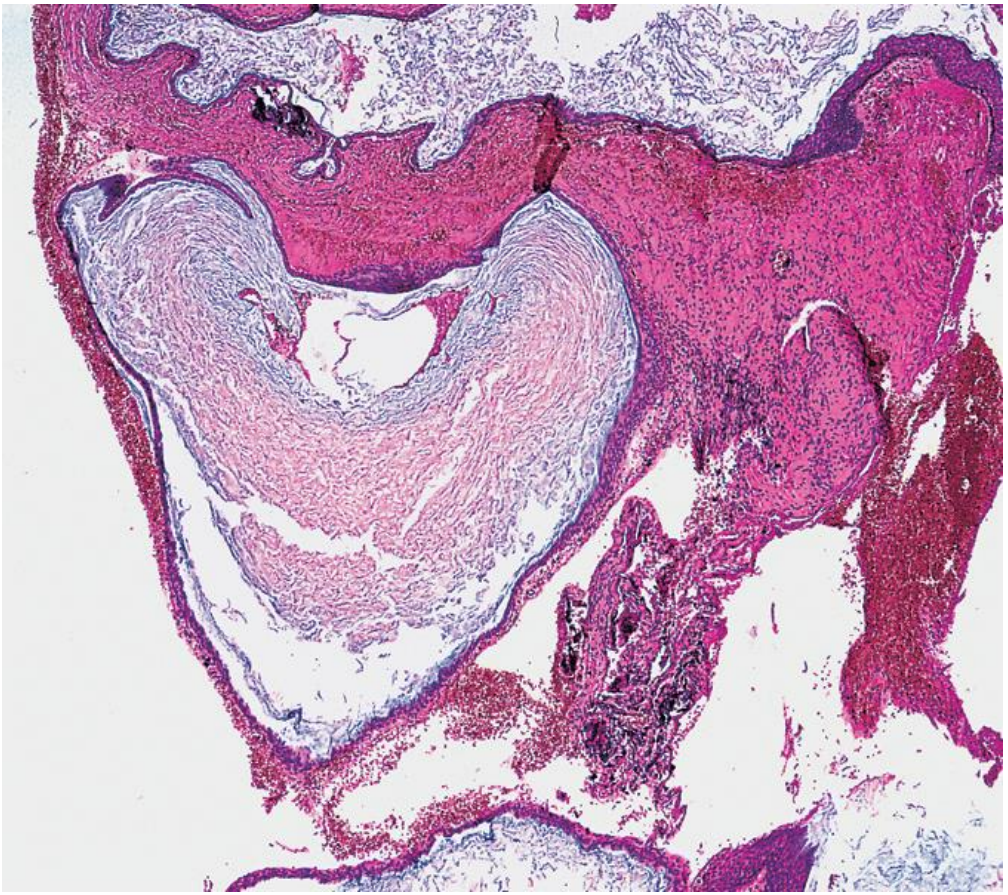
- Rare
- Occur at any age
- Occur anywhere in midline (including trunk and abdomen)
- Extremely aggressive
- Resembles squamous carcinoma morphologically
- BDR4-NUT fusion gene (chromatin regulation)
- Fusion protein induces terminal differentiation (a process seen in leukemia)

EARS

Cholesteatoma

- A locally aggressive cyst formed from epithelial rests and containing keratin centrally.
- It forms as a response to chronic inflammation.
- Such a cyst may perforate the tympanic membrane.
- Surgical excision is curative.

Cholesteatoma



A representative closed cholesteatoma is lined by stratified squamous epithelium which sheds keratinaceous debris in a radial, concentric fashion.

Fig. 16-71T

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

SALIVARY GLANDS

Cancer of salivary glands

- 3% of head and neck cancers
- Most common site is parotid.
- Most parotid tumors are benign, however.
- Sublingual and minor salivary gland cancers are rare; however, a minor salivary gland mass is usually malignancy.
- Swelling and pain at angle of jaw (if nerve entrapment) as presenting symptoms (parotid).
- Nerve entrapment usually associated with malignancy.

Disorders of salivary glands

- Most common tumor (60%) is pleomorphic adenoma (benign mixed tumor) of parotid.
- More common in women.
- Local recurrence 4%
- 2% develop malignancy over 5 year period.

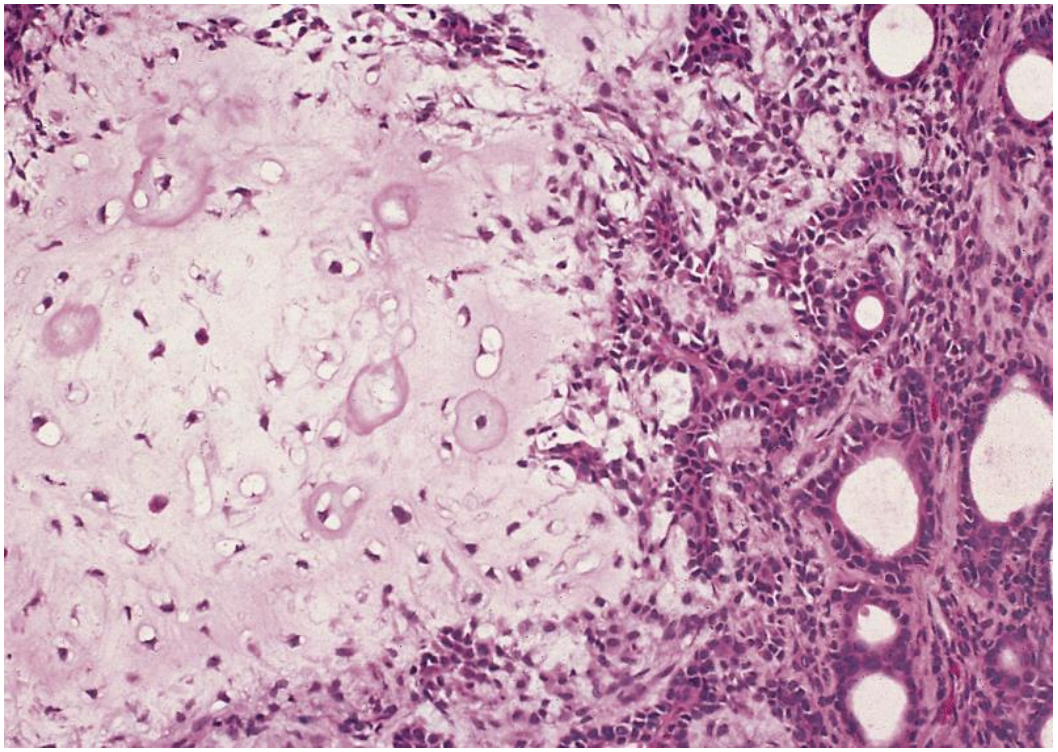
Pleomorphic adenoma

- Usually encapsulated
- Particularly in the palate the capsule is not fully developed, and expansile growth produces protrusions into the surrounding gland, which may lead to recurrences if the tumor is merely enucleated.
- The cut surface is gray-white with myxoid and blue translucent areas of chondroid (cartilage-like) material.

Pleomorphic adenoma

- Epithelial elements resembling ductal cells or myoepithelial cells are arranged in duct formations, acini, irregular tubules, strands, or sheets of cells.
- These elements are typically dispersed within a mesenchyme-like background of loose myxoid tissue containing islands of cartilage and, rarely, foci of bone.
- In most cases there is no epithelial dysplasia or evident mitotic activity.
- There is no difference in biologic behavior between the tumors composed largely of epithelial elements and those composed of myoepithelial cells.

Mixed tumor (pleomorphic adenoma)



This prototypic mixed tumor has closely associated epithelial islands and ductal structures, and shows cartilaginous differentiation.

Generally encapsulated.

Fig. 4-8

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Disorders of salivary glands

- Second most common benign tumor of parotid is a lymphoepithelioma (Warthin's tumor).
- May represent salivary gland rests in lymph nodes or remnants of branchial pouches.
- Rarely are found arising in cervical lymph nodes.
- 10% bilateral and 10% multifocal.
- Found principally in smokers.
- Peak in 5^{th} to 7^{th} decades.
- More common in men.
- 2% recur.

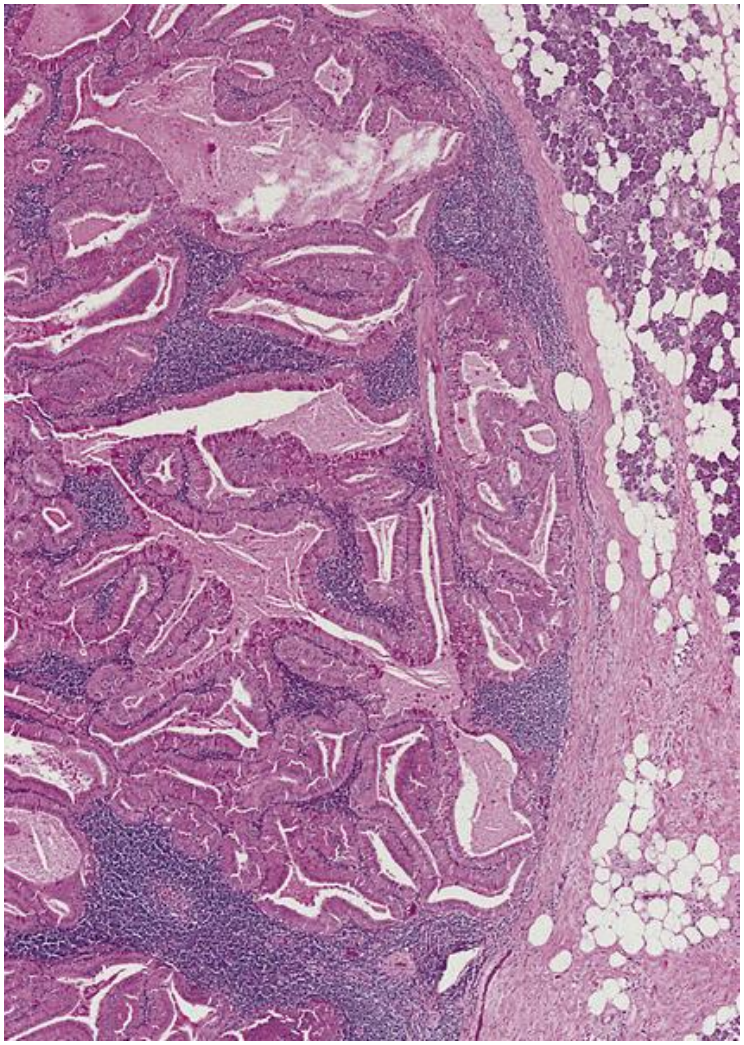
Warthin's tumor

- Round to oval encapsulated masses
- Usually arising in the superficial parotid gland
- Transection reveals a pale gray surface punctuated by narrow cystic or cleft-like spaces filled with mucinous or serous secretions.
- Histology:
- Cleft-like spaces are lined by a double layer of neoplastic epithelial cells resting on a dense lymphoid stroma sometimes bearing germinal centers.
- The spaces are frequently narrowed by polypoid projections of the lymphoepithelial elements.

Warthin's tumor

- The double layer of lining cells is distinctive:
- The upper layer consists of palisading columnar cells with abundant, finely granular, eosinophilic cytoplasm, while the lower layer is comprised of cuboidal to polygonal cells.
- Granularity a manifestation of multiple mitochondria in cytoplasm
- Secretory cells are dispersed in the columnar cell layer, accounting for the secretions within the dilated lumens.
- On occasion, there are foci of squamous metaplasia.

Warthin's tumor

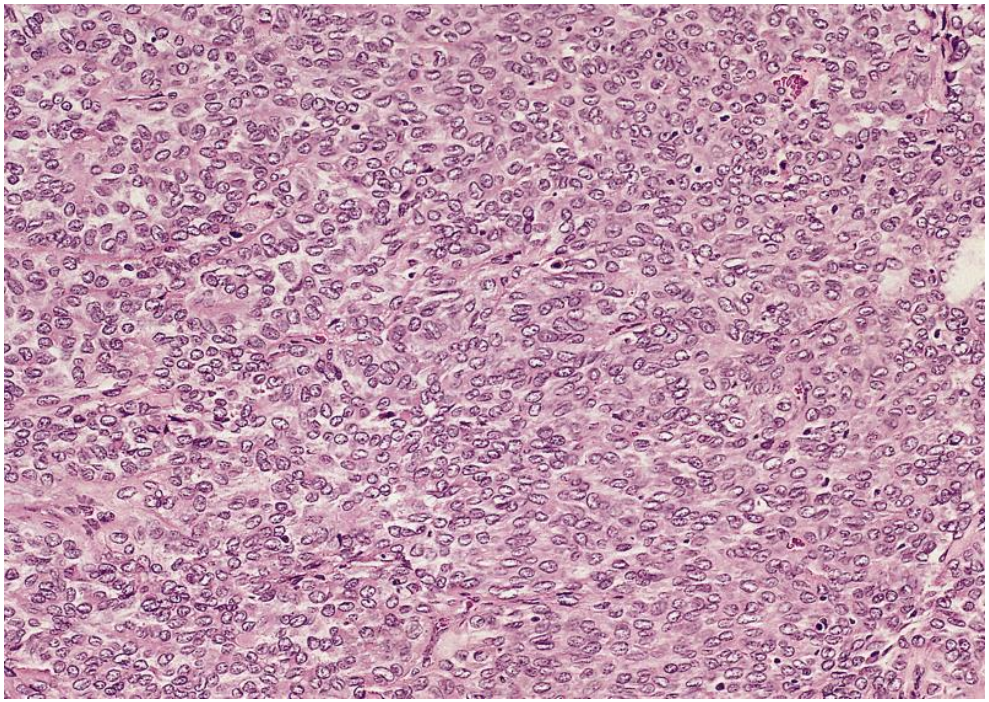


The luminal columnar cells are uniformly oriented and have slightly hyperchromatic nuclei. In palisade. Oncocytic change is identified. The basal cells appear less numerous, have round to ovoid nuclei with small but distinct nucleoli, and have ill- defined cytoplasmic borders. A dense lymphoid stroma is present. Germinal centers are noted.

Fig. 4-48

Ellis, Gary L, Auclair, Paul L., "Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Myoepithelioma



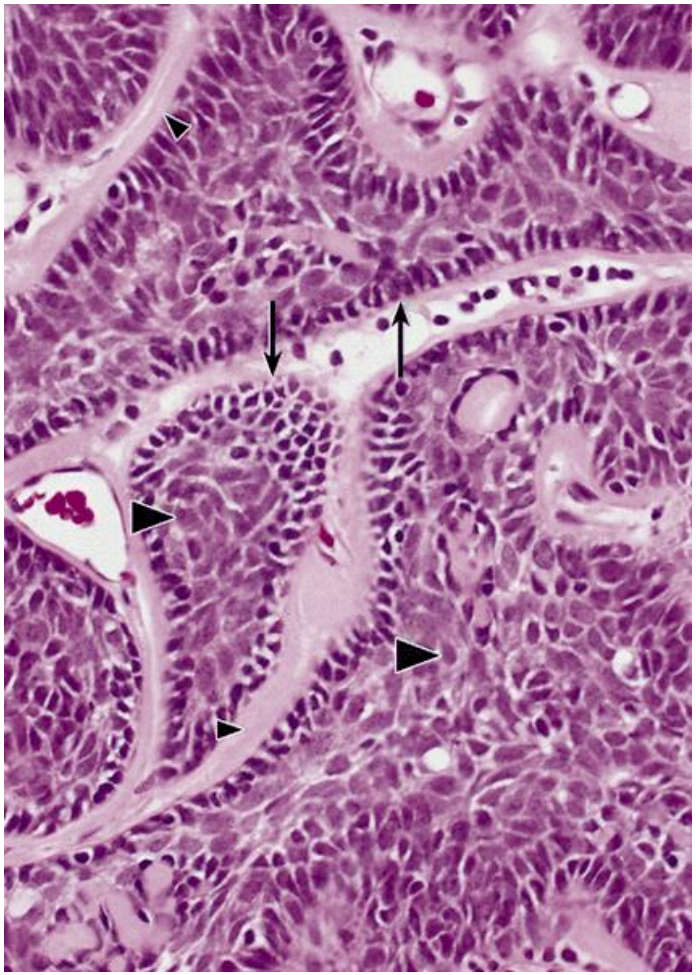
Compactly arranged cells with round, ovoid, and fusiform nuclei and very limited cytoplasm characterize this tumor.

5% have BRAF and PTH1 mutations

Fig. 4-36

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Basal cell adenoma

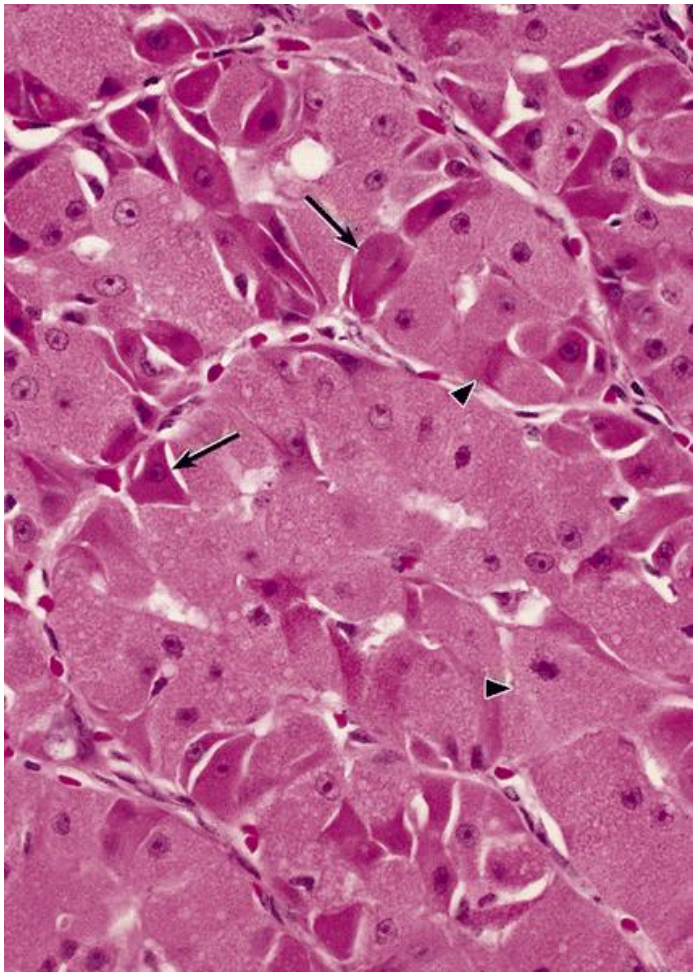


The tumor is composed of cells of two morphologic forms. Some cells, which are mostly located toward the periphery of the epithelial islands, have small, very basophilic nuclei and scant cytoplasm and impart a deeply basophilic (dark) appearance to the tissue in which they are aggregated (arrows). More numerous are larger cells with large, pale- staining nuclei (large arrowheads). Eosinophilic hyaline material is adjacent to the tumor islands (small arrowheads).

Fig. 4-63

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Oncocytoma



Large polygonal cells have prominent, granular eosinophilic cytoplasm and centrally placed nuclei with dispersed chromatin and nucleoli, usually single. The intensity of cytoplasmic staining is variable, and darker (arrows) and lighter (arrowheads) cells can be identified.

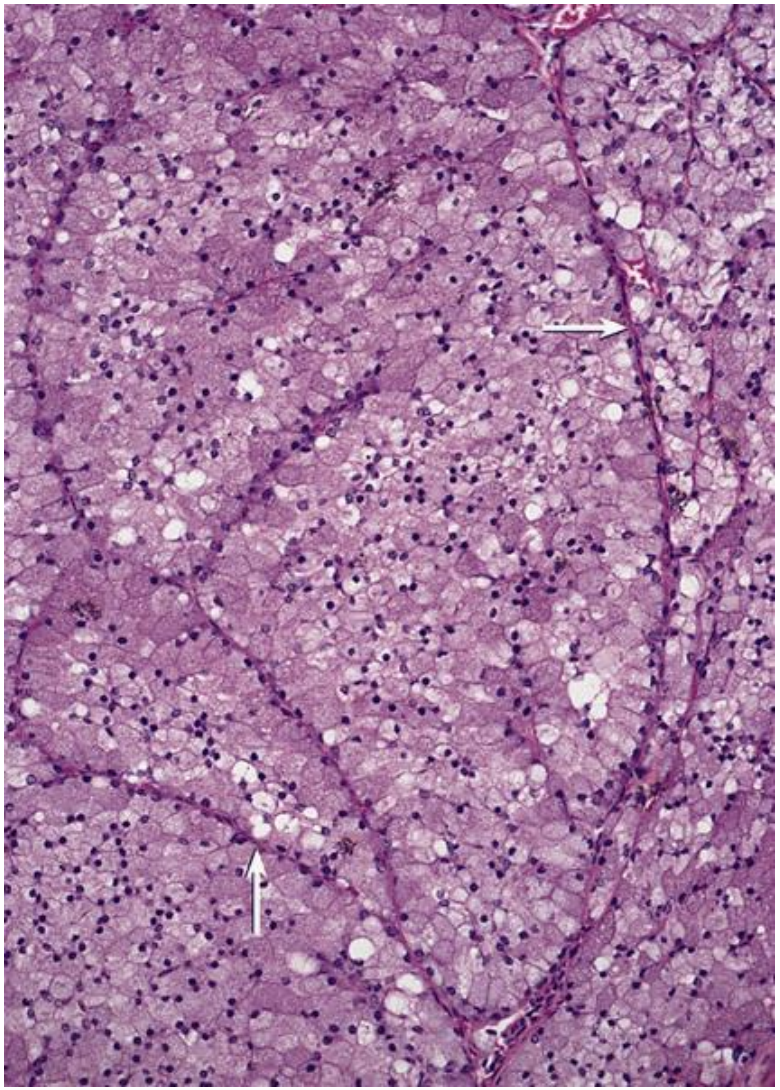
Fig. 4-99

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Cancer of salivary glands

- Acinic cell carcinoma
- <3% all salivary gland malignant tumors.
- Sometimes bilateral and multicentric.
- Slow growing.
- >80% survival following resection.
- 5% BRAF mutations
- 5-10% have elevated tumor mutational burden (TMB)

Acinic cell carcinoma



Neoplastic acinar cells are large, round to polygonal cells with granular, slightly basophilic cytoplasm and dark, round, eccentrically located nuclei.

Fig. 5-42

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Cancer of salivary glands

- Adenocarcinoma
- 16% of parotid cancers, 9% of submandibular cancers.
- 50-80% HER2+
- 40-50% overexpress Androgen Receptor (AR)
- 5% BRAF mutations
- 5-10% have elevated tumor mutational burden (TMB)
- 76% survival (correlates with grade)

Cancer of salivary glands

- Salivary duct carcinoma
- 50-80% HER2+
- 40-50% overexpress Androgen Receptor (AR)
- 5-10% have elevated tumor mutational burden (TMB)
- If significant disease following resection, trastuzumab and docetaxel chemotherapy
- Trastuzumab exestane as other option
- Secretory carcinoma
- NTRK3-ETV6 fusion diagnostic
- Respond to entrectinib, larotrectinib

Cancer of salivary glands

- Mucoepidermoid carcinoma is most common malignancy of parotid (60-70%).
- Aggressive.
- Rarely metastasize.
- 50% show a balanced t(11;19)(q21;p13) abnormality that produces a MECT1-MAML2 fusion gene in which the CREB c-AMP binding domain is fused to the Notch domain co-activator.
- 5-10% have elevated tumor mutational burden (TMB)
- Surgical resection
- Carboplatin with paclitaxel chemotherapy if metastasizes

Mucoepidermoid carcinoma

- Lack well-defined capsules
- Often infiltrative at the margins.
- Pale and gray-white on transection, they frequently contain small, mucin-containing cysts.
- The basic histologic pattern is that of cords, sheets, or cystic configurations of squamous, mucous, or intermediate cells.
- Vary from well-differentiated to anaplastic.
- Survival 76% if low grade
- 30% if high grade.

Mucoepidermoid carcinoma

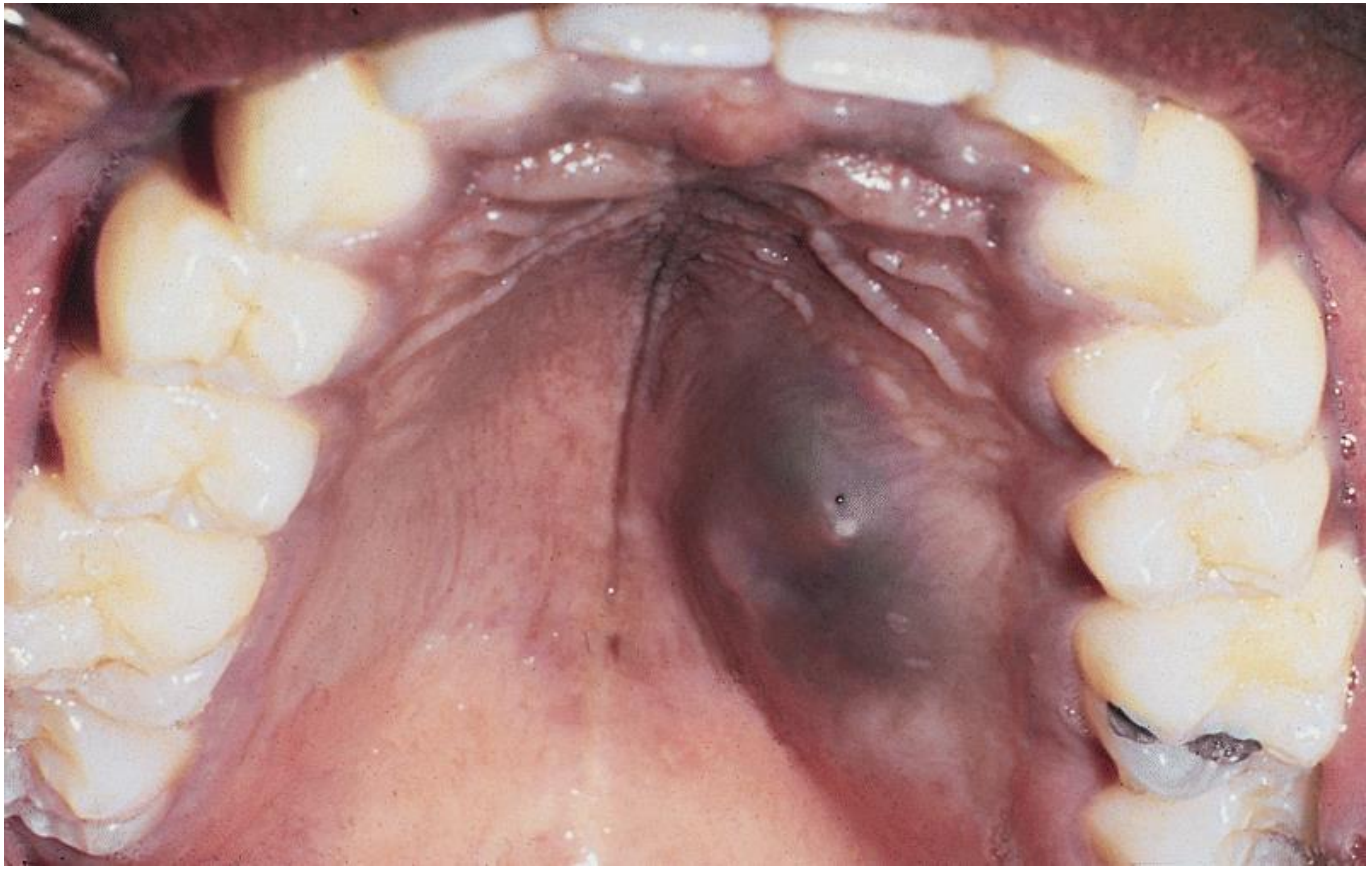
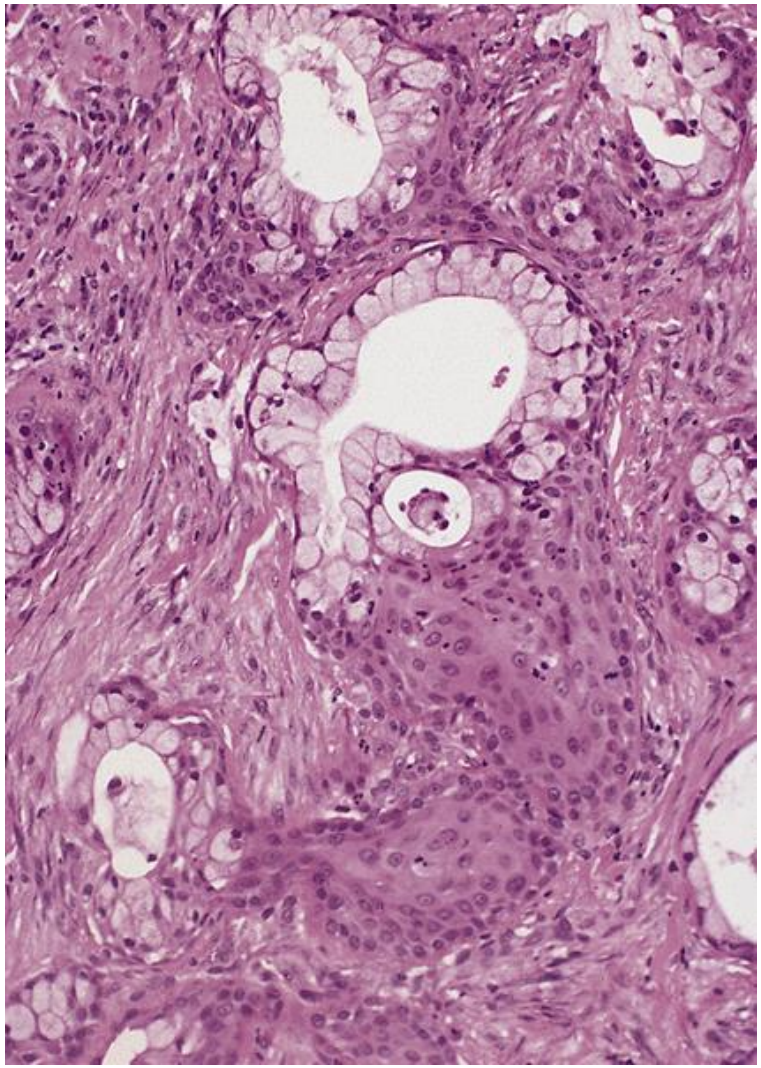


Fig. 5-1

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Mucoepidermoid carcinoma



The close association of mucous and epidermoid cells is characteristic of mucoepidermoid carcinoma.

Fig. 5-2

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

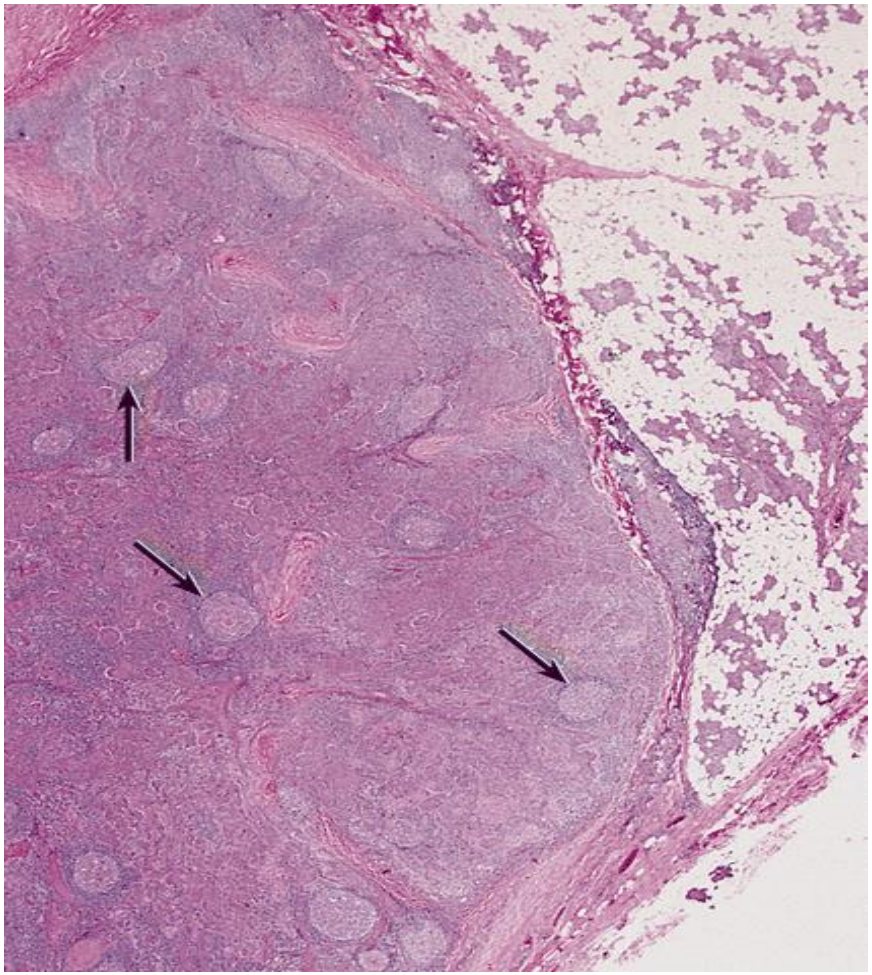
Cancer of salivary glands

- Squamous cell carcinomas are 7% of parotid and 10% of submandibular gland cancers.
- 5-10% have elevated tumor mutational burden (TMB)
- Resect
- Carboplatin with paclitaxel chemotherapy
- Grade correlates with survival.
- Survival 24%.
- Squamous cancer of surrounding skin may metastasize to parotid and be confused with primary cancer.

Cancer of salivary glands

- Lymphoepithelial cancer is a squamous cancer in a lymphoid stroma.
- The usual malignancy arising from a Warthin's tumor is a lymphoma.

Lymphoepithelial carcinoma

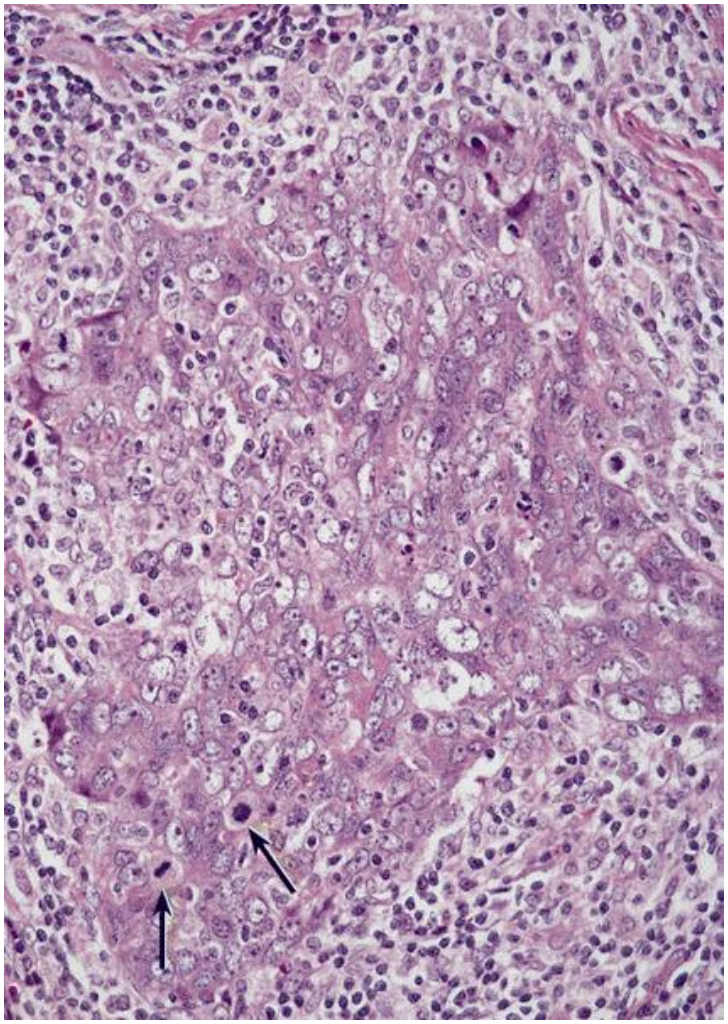


Solid squamous islands and duct-like structures are seen within dense lymphocytic stroma that shows several well-developed lymphoid follicles.

Fig. 5-241

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

Lymphoepithelial carcinoma



A syncytial mass of undifferentiated epithelial cells is within a lymphoid stroma. The cells have indistinct cell boundaries, round vesicular nuclei, and prominent nucleoli. Several mitotic figures are present in this field (arrows).

Fig. 5-245

Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

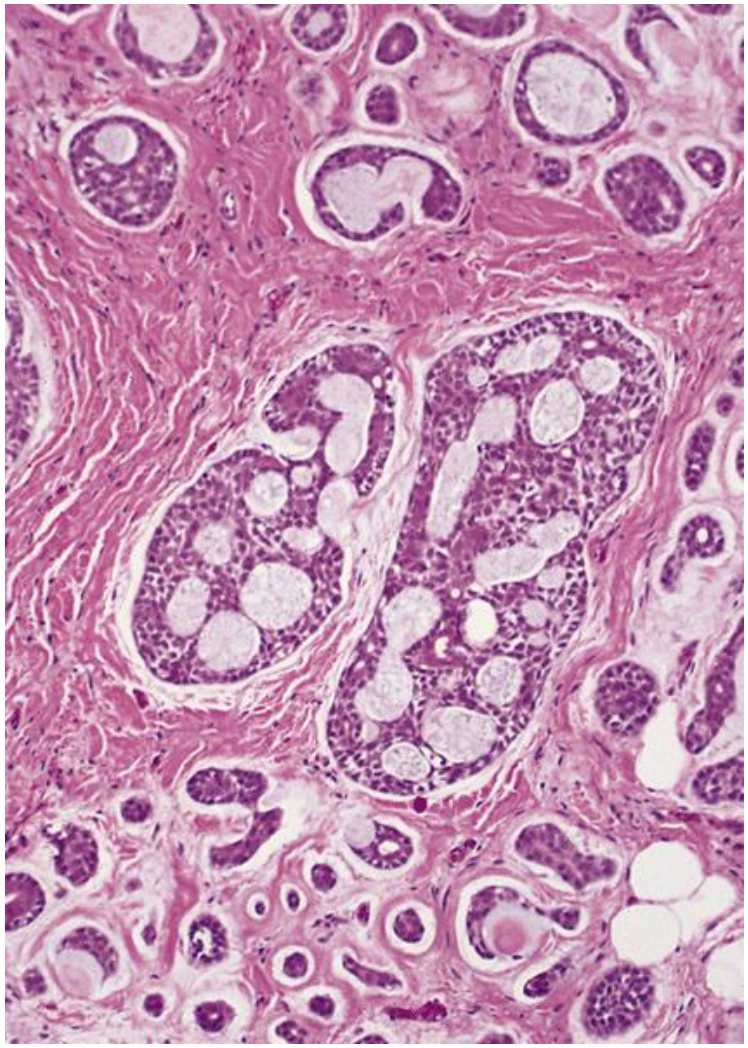
Cancer of salivary glands

- Adenoid cystic carcinoma is most common malignant tumor of submandibular gland (41%) but only 11% of parotid cancers.
- MYB-NF1B in 60-70%
- NOTCH gain of function in 18-30%
- 40% develop metastases.
- Visceral (other than lung) and bone metastases are poor prognostic signs.
- May respond to tyrosine kinase inhibitor
- Survival 50%.

Adenoid cystic carcinoma

- Small, poorly encapsulated, infiltrative, gray-pink lesions
- Composed of small cells having dark, compact nuclei and scant cytoplasm.
- These cells tend to be disposed in tubular, solid, or cribriform patterns reminiscent of cylindromas
- The spaces between the tumor cells are often filled with a hyaline material thought to represent excess basement membrane
- Tubular and solid variants are noted.

Adenoid cystic carcinoma



Various morphologic patterns commonly exist within a single neoplasm. A tubular pattern is evident at the top and bottom portion of the figure while a cribriform pattern with variable amounts of mucohyaline material is present in the center.

Fig. 5-72L

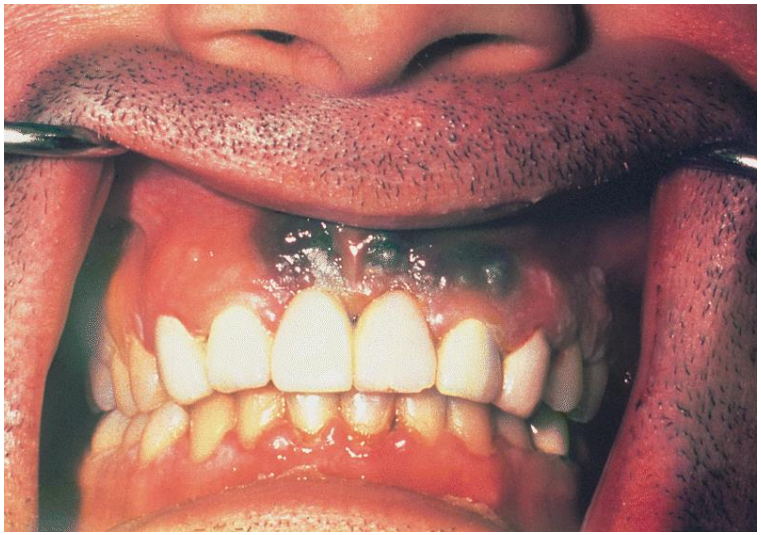
Ellis, Gary L, Auclair, Paul L., “Tumors of the salivary glands. Atlas of Tumor Pathology, Third Series, Fascicle 17. Armed Forces Institute of Pathology. Washington, D.C. (1996)

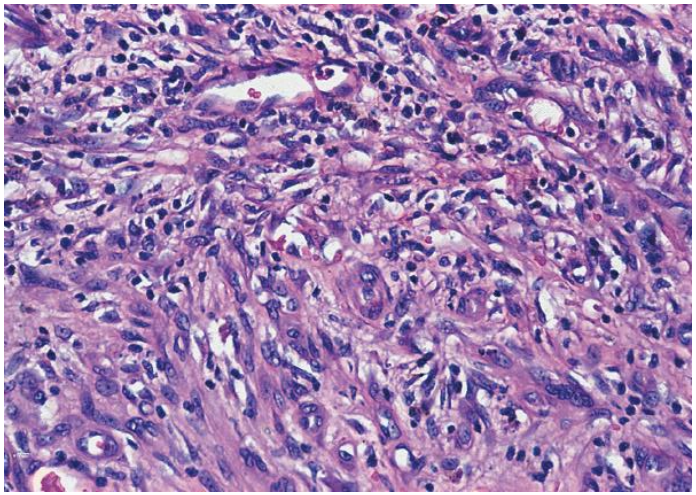
Cancer of salivary glands

- Malignant mixed tumor
- May develop in pleomorphic adenoma.
- 14% of parotid and 12% of submandibular gland cancers.
- 25% nodal metastases;
- 25% distant metastases.
- 5-10% have elevated tumor mutational burden (TMB)
- Resect
- Carboplatin with paclitaxel chemotherapy
- 30% survival.

OROPHARYNX

Kaposi’s sarcoma





Gingival involvement by Kaposi's sarcoma in this HIV-positive male produces multiple, deep blue nodules. (Gross) Nodular Kaposi's sarcoma consists of proliferating spindle cells, with scattered, often slit-like vascular spaces and some associated inflammation. (Microscopic)

Figs. 9-41 and 9-42

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Leukoplakia

- Generally males, ages 40-70 years
- Years of tobacco use.
- Occur anywhere in the oral cavity.
- Favored locations are floor of mouth, buccal mucosa, ventral surface of the tongue, palate, gingiva.

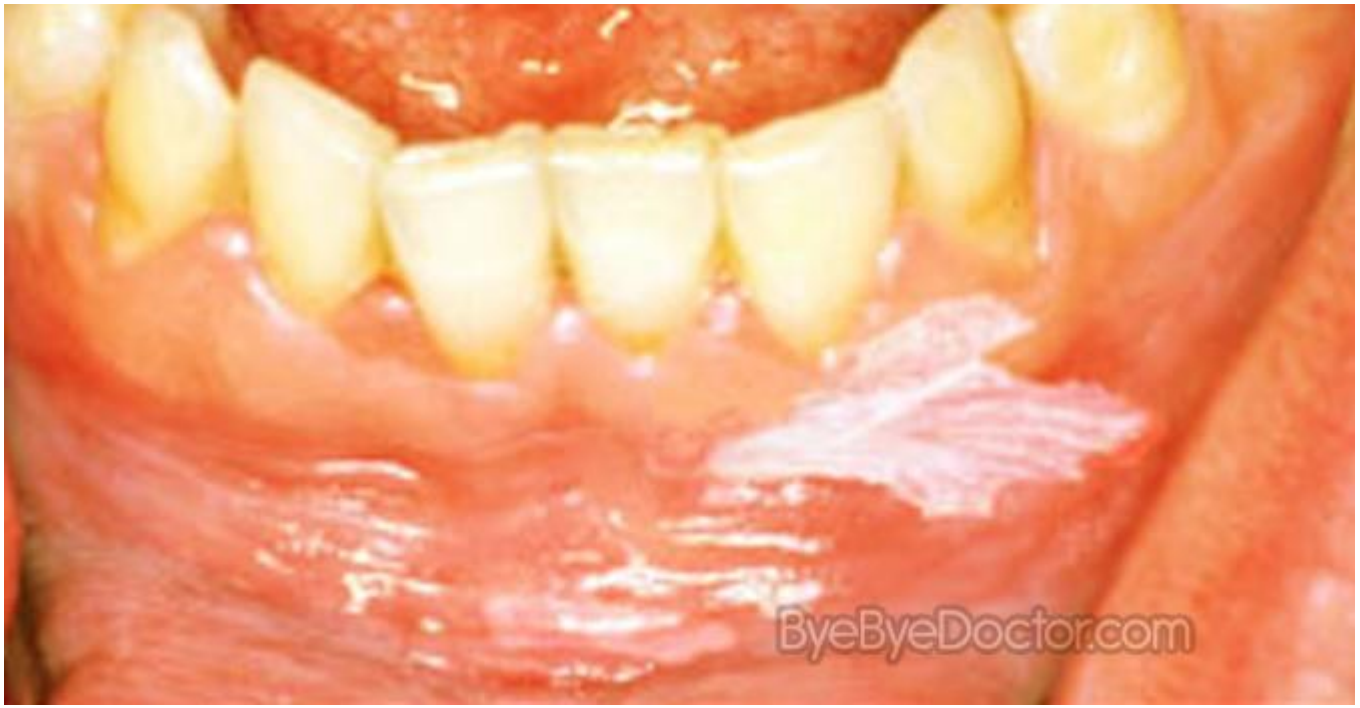
Leukoplakia

- May very from acanthosis and hyperkeratosis (demarcated white patch or plaque) to markedly dysplastic epithelium.
- Red, velvety, eroded mucosa is erythroplakia and carries high risk of malignancy.
- Hairy leukoplakia is fluffy.
- Associated with EBV infection in the immunocompromised.

Leukoplakia

- Leukoplakia presents a spectrum of epithelial changes ranging from hyperkeratosis overlying a thickened, acanthotic but orderly mucosal epithelium to lesions with markedly dysplastic changes sometimes merging into carcinoma in situ
- 90% of erythroplakia demonstrate severe dysplasia, carcinoma in situ, or minimally invasive carcinoma.
- Often, an intense subepithelial inflammatory reaction with vascular dilation is seen that likely contributes to the reddish clinical appearance.

Leukoplakia



https://byebyedoctor.com/wp-content/uploads/2011/05/leukoplakia-2.jpg
Accessed 1/22/2019

Malignant lesions of oral cavity

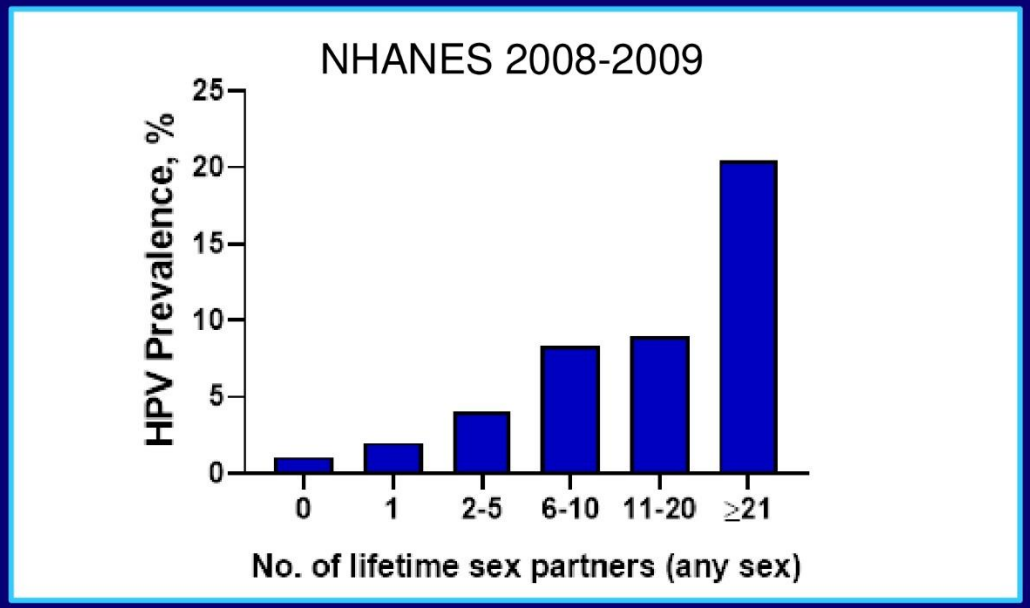
- Majority of tumors are squamous cell carcinoma
- More common in males
- Risk factors:
- Tobacco
- Pipe smoking associated with cancer of lip
- Alcohol (synergistic with tobacco, increasing relative risk thirty times)
- HPV 16 (70% of tumors)
- Chronic irritation (dentures)
- Actinic radiation (sunlight) associated with cancer of lip

Head and Neck Cancer Stratification

	HPV-positive	HPV-negative
Anatomic site	Tonsil / BOT	All sites
Histology	Basaloid	Keratinized
Age	Younger	Older
Gender	3:1 men	3:1 men
SE status	High	Low
Risk factors	Sexual behavior	Alcohol / tobacco
Cofactors	Marijuana, immunosuppression	Diet, hygiene
Genetics	p53WT, p16 +	p53Mu, p16-
Incidence	Increasing	Decreasing
Survival	High	Worse

Gillison M JNCI 2000; Gillison, JNCI 2008

Sexual Behavior and Oral HPV Infection



Gillison M et al , JAMA 2012

Malignant lesions of oral cavity

- Poor tumor grade and an oropharyngeal site independently increased the probability of the presence of HPV.
- Oropharyngeal tumors are more likely to be HPV positive (57%) compared with oral cavity (12%) tumor sites and non-oropharyngeal (14%) sites.
- HPV-positive oropharyngeal cancers predominantly arise in the palatine or lingual tonsils.
- For tonsil or base-of-tongue sites, 62% of tumors were HPV positive, compared with 25% for other oropharyngeal sites.

Malignant lesions of oral cavity

- Extranodal extension added to staging
- Staging separated by HPV involvement
- The risk of developing a second primary tumor in patients with tumors of the upper aerodigestive tract has been estimated to be 3% to 7% per year.
- Cetuximab with radiation inferior to chemotherapy with radiation with locally advanced HPV oral-pharyngeal cancer but not HPV negative in oropharynx

Table 1. Characteristics Associated With the Risk of Oropharyngeal Cancer[a]

Degree of Risk	Characteristics	3-y OS Rate
Low	HPV+, smoking history of ≤10 pack-years, and N0–N2a nodal history	93% (95% CI, 88.3%–97.7%)
Intermediate	HPV+, smoking history of >10 pack-years, and N2b–N3 nodal disease; or	70.8% (95% CI, 60.7%–80.8%)
	HPV-, smoking history of ≤10 pack-years, and N2b–N3 nodal disease or T2–T3 tumors	
High	HPV- and smoking history >10 pack-years; or	46.2% (95% CI, 34.7%–57.7%)
	HPV-, smoking history ≤10 pack-years, and T4 disease	

https://www.cancer.gov/types/head-and-neck/hp/adult/oropharyngeal-treatment-pdq#_397_toc

Risk factors

- Majority of tumors are squamous cell carcinoma
- More common in males
- Smoking history of more than 10 pack years and other tobacco use.
- Pipe smoking associated with cancer of lip
- Heavy alcohol use (synergistic with tobacco, increasing relative risk thirty times)
- Defective elimination of acetaldehyde
- Many East Asians have mutation that leads to ineffective alcoholic dehydrogenase-2

Risk factors

- HPV infection (70% of tumors)
- Chronic irritation (dentures)
- Actinic radiation (sunlight) associated with cancer of lip
- Chewing betel quid or paan

Malignant lesions of oral cavity

- Vermilion border of lower lip, floor of mouth, and lateral border of tongue most common sites (in descending order)
- These cancers begin as dysplastic lesions, which may or may not progress to full-thickness dysplasia (carcinoma in situ) before invading the underlying connective tissue stroma
- Degree of keratinization not related to behavior

Cancer of the lip

- Exophytic mass or ulcerative lesion, generally on the lower lip. Friable.
- Submandibular and submental nodes involved 5-10% of time.
- Upper lip tumors also go to preauricular region; metastasize earlier than lower lip tumors.
- Midline tumors spread bilaterally.
- Survival 84% T_1, T_2; 50% if nodes involved.

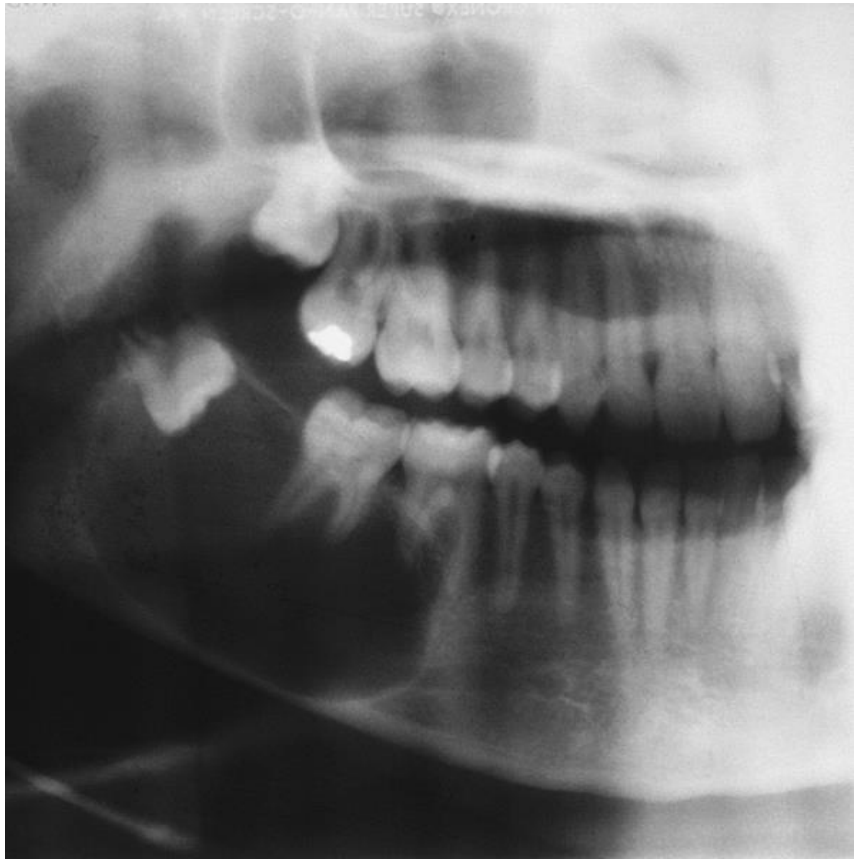
Table 16-3 Histologic Classification of Odontogenic Tumors

Tumors of odontogenic epithelium
Benign
Ameloblastoma
Calcifying epithelial odontogenic tumor (Pindborg tumor)
Squamous odontogenic tumor
Adenomatoid odontogenic tumor
Malignant
Ameloblastic carcinoma
Malignant ameloblastoma
Clear-cell odontogenic carcinoma
Ghost cell odontogenic carcinoma
Primary intraosseous squamous cell carcinoma
Tumors of odontogenic ectomesenchyme
Odontogenic fibroma
Odontogenic myxoma
Cementoblastoma
Tumors of odontogenic epithelium and ectomesenchyme
Benign
Ameloblastic fibroma
Ameloblastic fibro-odontoma
Adenomatoid odontogenic tumor
Odontoameloblastoma
Complex odontoma
Compound odontoma
Calcifying cystic odontogenic tumor (calcifying odontogenic cyst)
Dentinogenic ghost cell tumor
Malignant
Ameloblastic fibrosarcoma

Odontogenic tumors

- Ameloblastoma arises from odontogenic epithelium and shows no ectomesenchymal differentiation.
- Commonly cystic, slow growing, and locally invasive.
- Odontoma, the most common type of odontogenic tumor, arises from epithelium but shows extensive depositions of enamel and dentin.
- Odontomas are probably hamartomas

Ameloblastoma

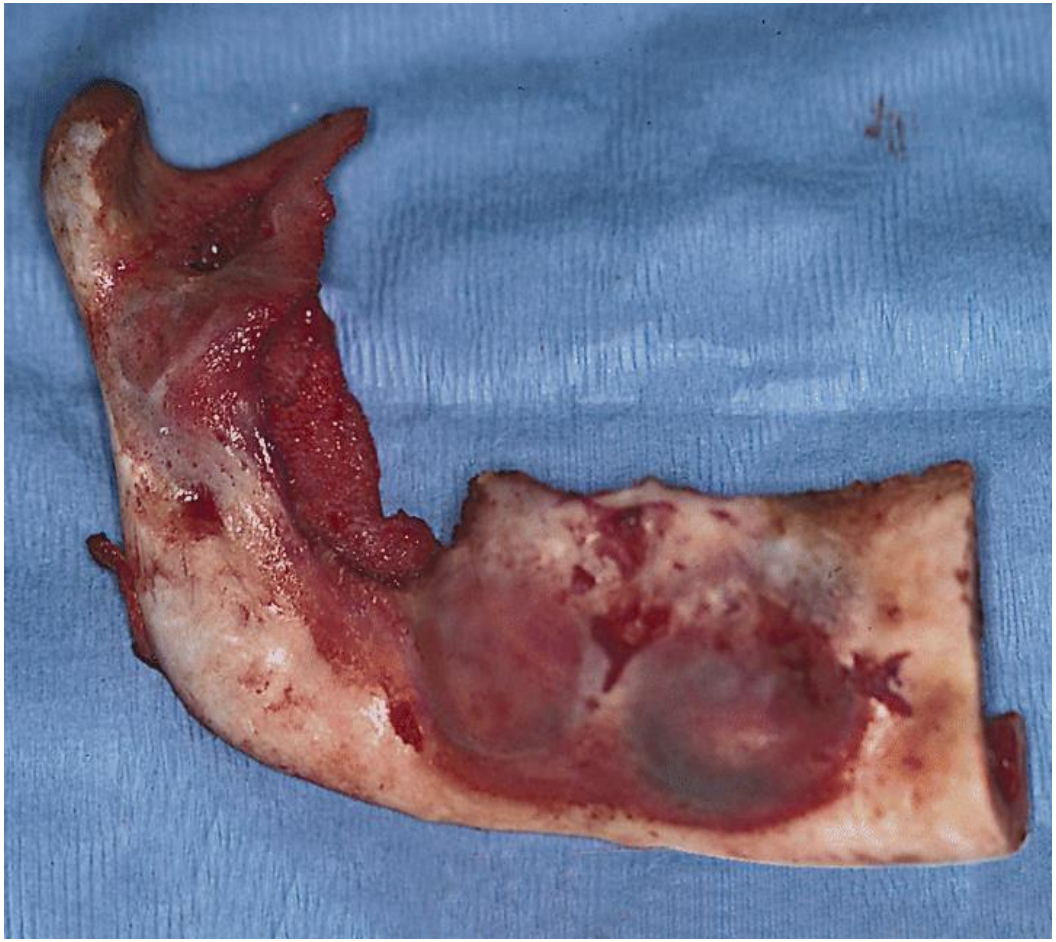


This panoramic radiograph demonstrates posterior displacement of an unerupted third molar situated at the superior pole of a discrete unilocular radiolucency. The lesion
occupies the posterior body of the mandible and extends into the ramus.

Fig. 5-1

Sciubba, James J, Fantasia, John E, Kahn, Leonard B., “Tumors and cysts of the jaws.” Atlas of Tumor Pathology, Third Series, Fascicle 29. Armed Forces Institute of Pathology. Washington, D.C. (2001)

Ameloblastoma



A multilobulated solid form of ameloblastoma occupies much of the body of the mandible and extends into the ramus and subcondylar regions, elevating the floor of the sigmoid notch.

Fig. 5-17

Sciubba, James J, Fantasia, John E, Kahn, Leonard B., “Tumors and cysts of the jaws.” Atlas of Tumor Pathology, Third Series, Fascicle 29. Armed Forces Institute of Pathology. Washington, D.C. (2001)

Ameloblastoma

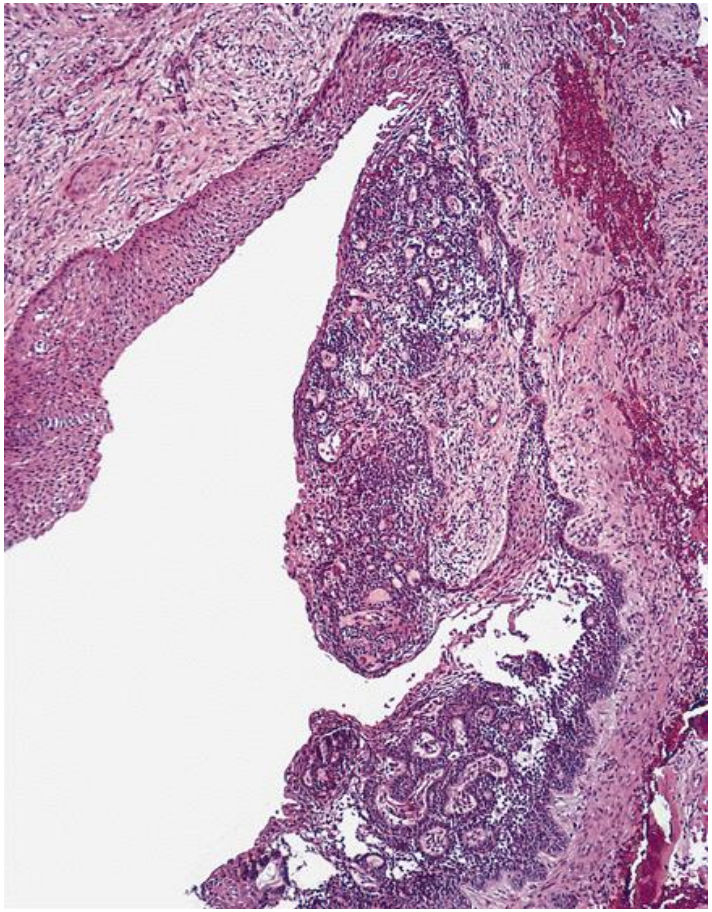


Fig. 5-7

Sciubba, James J, Fantasia, John E, Kahn, Leonard B., “Tumors and cysts of the jaws.” Atlas of Tumor Pathology, Third Series, Fascicle 29. Armed Forces Institute of Pathology. Washington, D.C. (2001)

A detailed view of a lining of unicystic ameloblastoma features a hyperchromatic basal and parabasal cell lining in association with an expanded compartment of stellate cells upon which is superimposed parakeratinized squamous lining epithelium.

The underlying connective tissue is moderately cellular and free of any invading or advancing epithelial proliferation.

Transition from squamous lining to nodular proliferation into the cyst lumen as well as proliferation into the surrounding connective tissue layer occurs.

Head and neck cancer

- Sarcomas are rare.
- Commonly present as submucosal or subcutaneous painless mass.
- In the hypopharynx or nasopharynx may present with cranial nerve abnormalities.
- Locally aggressive.
- High risk for metastases.
- En bloc dissection followed by radiation.

Head and neck cancer

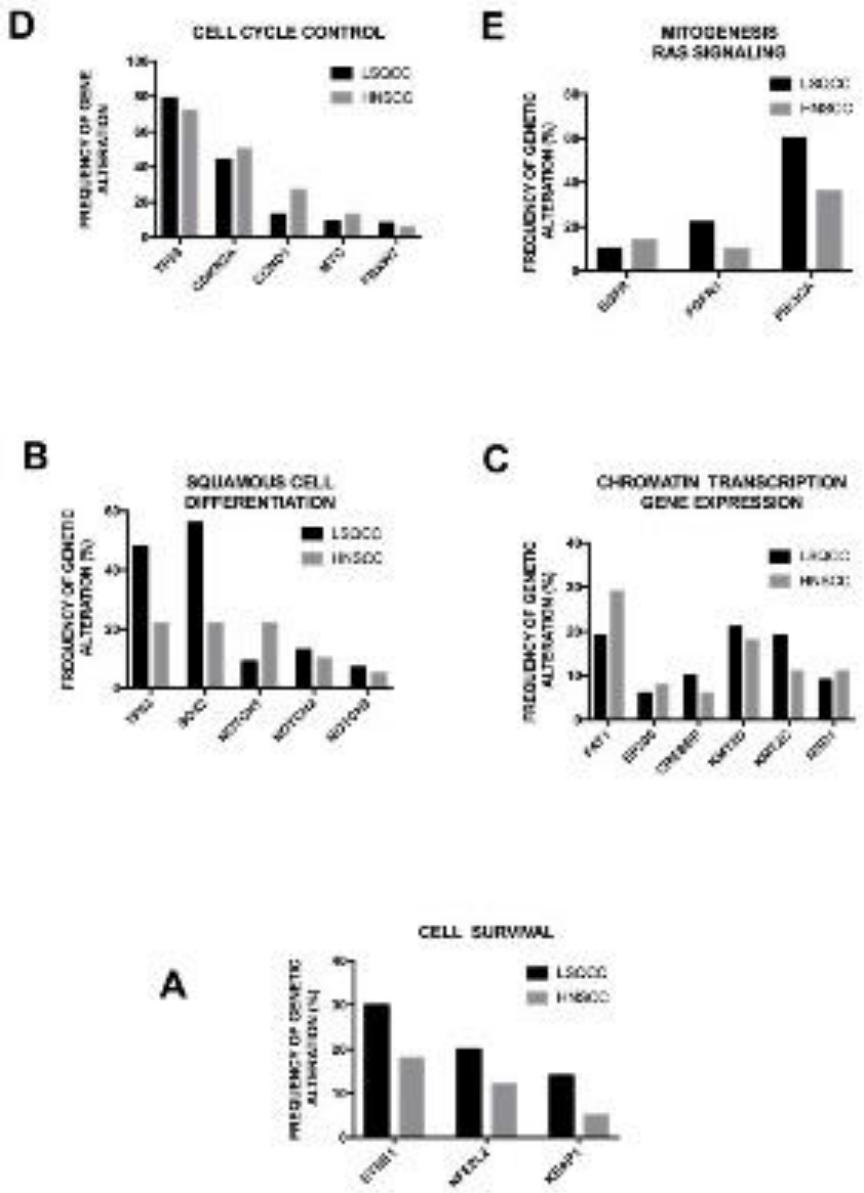
- Osteosarcoma of the jaw may benefit from chemoradiation.
- Melanomas principally seen in hard palate.
- Amelanotic.
- Median age 70 years old.
- 48% positive nodes.
- Aggressive.
- 17% survival.
- Surgery followed by brachytherapy.

Diagnosis of head and neck cancer

- If squamous carcinoma is suspected, excisional biopsy of a neck mass is contraindicated.
- Fine needle biopsy provides similar diagnostic information.
- Excisional biopsy complicates local control of the tumor and may promote metastases. It adds no information to treatment planning. Inspection of the nasopharynx and larynx is still required.
- CT and MRI are used for treatment planning.

Genetic model of oral cancer

- Stepwise progression.
- 9p21 (p16), 3p mutation prior to dysplastic change.
- 17p13 (p53) mutation prior to severe dysplastic change.
- 11q13 (cyclin D), 4q, 6p, 8p, 13q, 14q mutations prior to development of squamous cell carcinoma.
- HPV present in 50% of lesions (better prognosis if incorporated into cancer genome)
- HPV- tumors do not benefit from radiosensitizer



[Figure 3](#)

Pattern of frequently altered genes in Lung and Head and Neck squamous cell carcinoma subdivided according to their biologic function. A: Cell Survival; B: Squamous Cell Differentiation; C. Chromatin Transcription Gene Expression; D: Cell Cycle Control; E: Mitogenesis, RAS Signaling.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6116004/

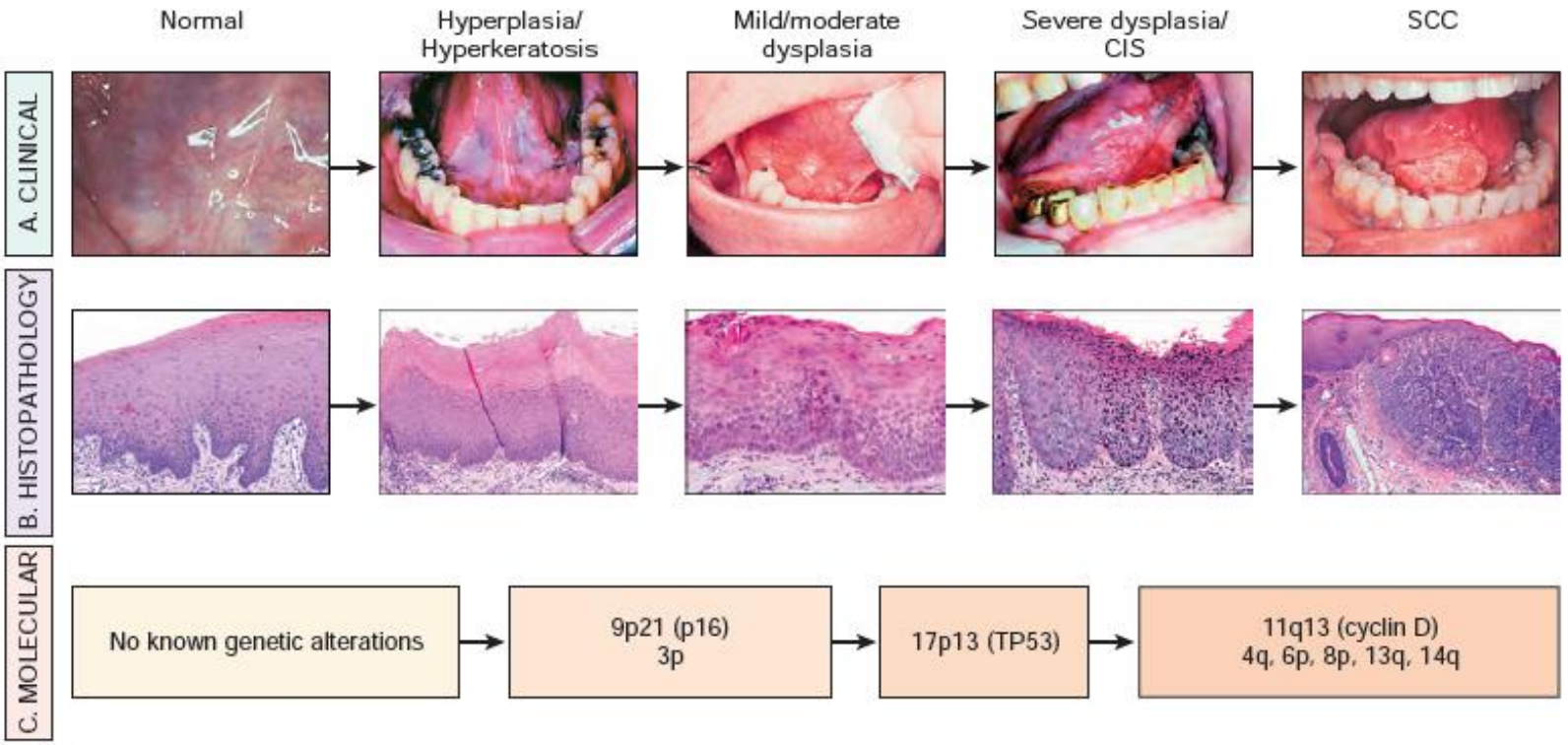


Figure 16-6 Clinical, histologic, and molecular progression of oral cancer. A, An idealized representation of the clinical progression of oral cancer. **B,** The histologic progression of squamous epithelium from normal, to hyperkeratosis, to mild/moderate dysplasia, to severe dysplasia, to cancer. **C,** The sites of the most common genetic alterations identified as important for cancer development. CIS, Carcinoma in situ; SCC, squamous cell carcinoma. (Clinical photographs courtesy of Sol Silverman, MD, from Silverman S: Oral Cancer. Hamilton, Ontario, Canada, BD Dekker, 2003.)

Metastatic sites

- The base of the tongue (47%) and the tonsil (46%) were the most common primary sites that metastasized to retro-pharynx.
- Most patients had stage T1 to T2 primary tumors (64%) and stage III to IVB disease (94%).

Metastatic sites

- The incidence of radiographic retropharyngeal node involvement was 10% and was highest for the pharyngeal wall (23%) and lowest for the base of the tongue (6%).
- Retropharyngeal lymph node involvement was associated with inferior 5-year local control and inferior recurrence-free survival, distant metastases−free survival, and overall survival on multivariate analysis.

Cancer of the alveolar ridge and the retromolar trigone

- 10% of all oral cancers.
- Exophytic mass or infiltrating tumor (may invade bone).
- Bleeding.
- Pain exacerbated by chewing.
- Loose teeth or ill-fitting dentures noted.
- 30% have positive nodes (70% if T_4).
- Survival >80% if T_1,T_2; 60%, T_3; 20%, T_4.

Granular cell tumor of tongue

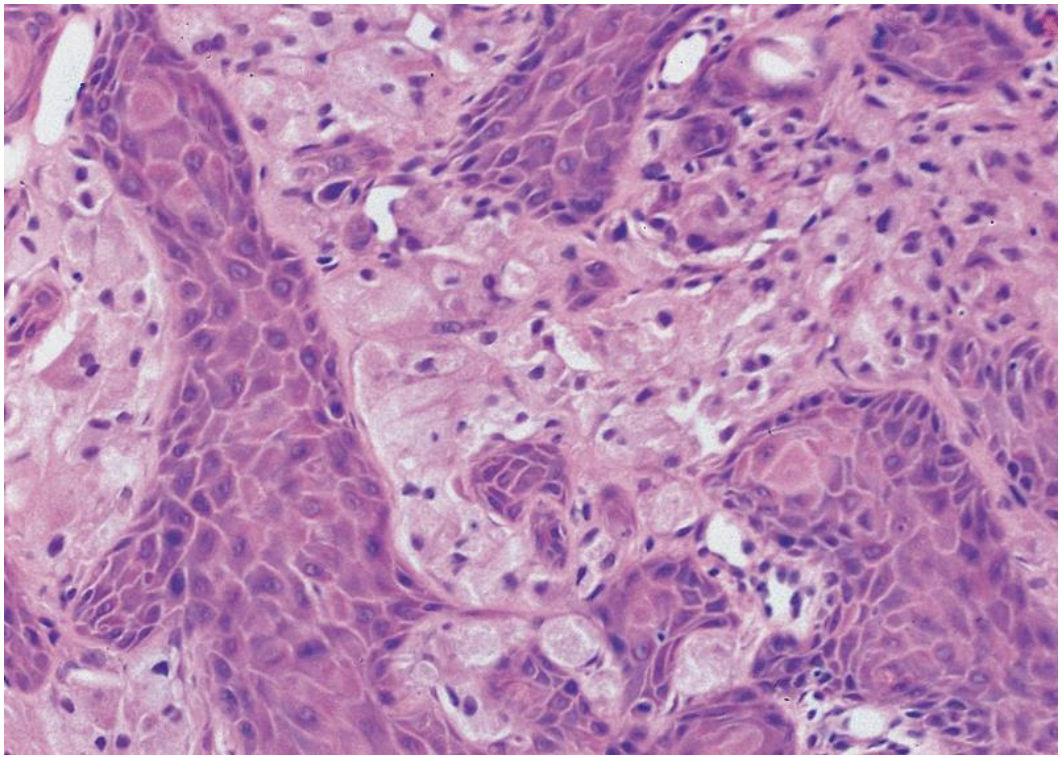


Fig. 3-30

Mills, SE, Gaffey, MJ, Frierson ,HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Pseudoepitheliomatous hyperplasia associated with an underlying
granular cell tumor of the tongue. Granular cell tumors are composed of sheets, nests, and clusters of tumor cells separated by a delicate, fibrovascular stroma. The tumor cells are large, polygonal, and
uniform, with distinct cellular borders and abundant granular eosinophilic cytoplasm. The nuclei are small and hyperchromatic. May be confused with squamous carcinoma clinically.

Cancer of the floor of the mouth

- 10-15% of oral cancers.
- 60 years old median age.
- Painful infiltrative lesions may invade bone, muscles of the floor of the mouth and tongue.
- Nodal involvement 12% (T_1), 30% (T_2), 47% (T_3); 53% (T_4). Go to level I and II nodes.
- Stage I, II survival >80%; III, 66%; IV, 32%.

Cancer of the anterior two-thirds of the tongue

- 60 years old median age.
- Exophytic or infiltrative. Pain. Occasional difficulty in speech and swallowing.
- Bilateral involvement 25%; level II nodes more common.
- Survival early stage, node negative, 70%; advanced stage, node positive, 32%.

Cancer of the hard palate

- 5% of oral cavity tumors
- 50%, squamous carcinomas; 50%, salivary gland tumors
- Deeply infiltrating or superficially spreading. Painful.
- 6-29% nodal involvement.
- Survival 75% stage I; 46%, stage II; 36%, stage III; 11% stage IV.

Cancer of the buccal mucosa

- 8% of oral cancers.
- Unlike other head and neck cancers, this occurs particularly in women.
- Silent presentation.
- Exophytic.
- Pain, bleeding, difficulty in chewing.
- 10% nodal involvement (levels I and II).
- Survival 77% in low stage; 18%, high stage.

Cancer of the hypopharynx

- Aggressive.
- Present as neck mass.
- 60% positive nodes at diagnosis. Occult metastases to thyroid and paratracheal node chain.
- Neck stiffness (retropharyngeal nodes)
- Otalgia (CN IX-X involvement).
- High risk of distant metastases.
- Survival 40% T_1, T_2; 16% T_3, T_4.

Cancer of the tonsillar pillar, tonsillar fossa, and soft palate

- 75% of tonsillar fossa tumors stage III of IV at presentation
- 55% with N_2 or N_3 disease
- Pain, dysphagia, weight loss, neck mass
- 38% of tonsillar pillar lesions are T_2.
- Survival ranges from 93% (stage I) to 17% (stage IV)
- Soft palate lesions present as erythroplakia.
- Indolent.
- Survival 85% (stage I) to 21% (stage IV)

Cancer of the posterior pharyngeal wall

- Advanced at diagnosis (silent).
- Pain, bleeding, weight loss.
- Neck mass is common initial sign.
- 25% T_1 have palpable nodes; >66% T_3, T_4
- Bilateral nodal involvement common.
- Survival >70% stage I, II; 42%, stage III; 27%, stage IV.

Cancer of the floor of the mouth

- 10-15% of oral cancers.
- 60 years old median age.
- Painful infiltrative lesions may invade bone, muscles of the floor of the mouth and tongue.
- Nodal involvement 12% (T_1), 30% (T_2), 47% (T_3); 53% (T_4). Go to level I and II nodes.
- Stage I, II survival >80%; III, 66%; IV, 32%.

Cancer of the anterior two-thirds of the tongue

- 60 years old median age.
- Exophytic or infiltrative.
- Pain.
- Occasional difficulty in speech and swallowing.
- Bilateral involvement 25%; level II nodes more common.
- Survival early stage, node negative, 70%; advanced stage, node positive, 32%.

Cancer of the base of the tongue

- Advanced at presentation generally.
- Pain, dysphagia, weight loss, and otalgia (Cranial Nerve IX-X involvement).
- Neck mass is frequent presentation.
- 70-80% nodal involvement.
- Survival 60%, stage I; 40%, stage II; 30%, stage III; 15%, stage IV

Cancer of the hypopharynx

- Aggressive.
- Present as neck mass.
- 60% positive nodes at diagnosis. Occult metastases to thyroid and paratracheal node chain.
- Neck stiffness (retropharyngeal nodes); otalgia (CN X involvement).
- High risk of distant metastases.
- Survival 40% T_1, T_2; 16% T_3, T_4.

Cancer of the tonsilar pillar, tonsilar fossa, and soft palate

- 75% of tonsillar fossa tumors stage III of IV at presentation
- 55% with N_2 or N_3 disease
- Pain, dysphagia, weight loss, neck mass
- 38% of tonsillar pillar lesions are T_2.
- Survival ranges from 93% (stage I) to 17% (stage IV)
- Soft palate lesions present as erythroplakia. Indolent.
- Survival 85% (stage I) to 21% (stage IV)

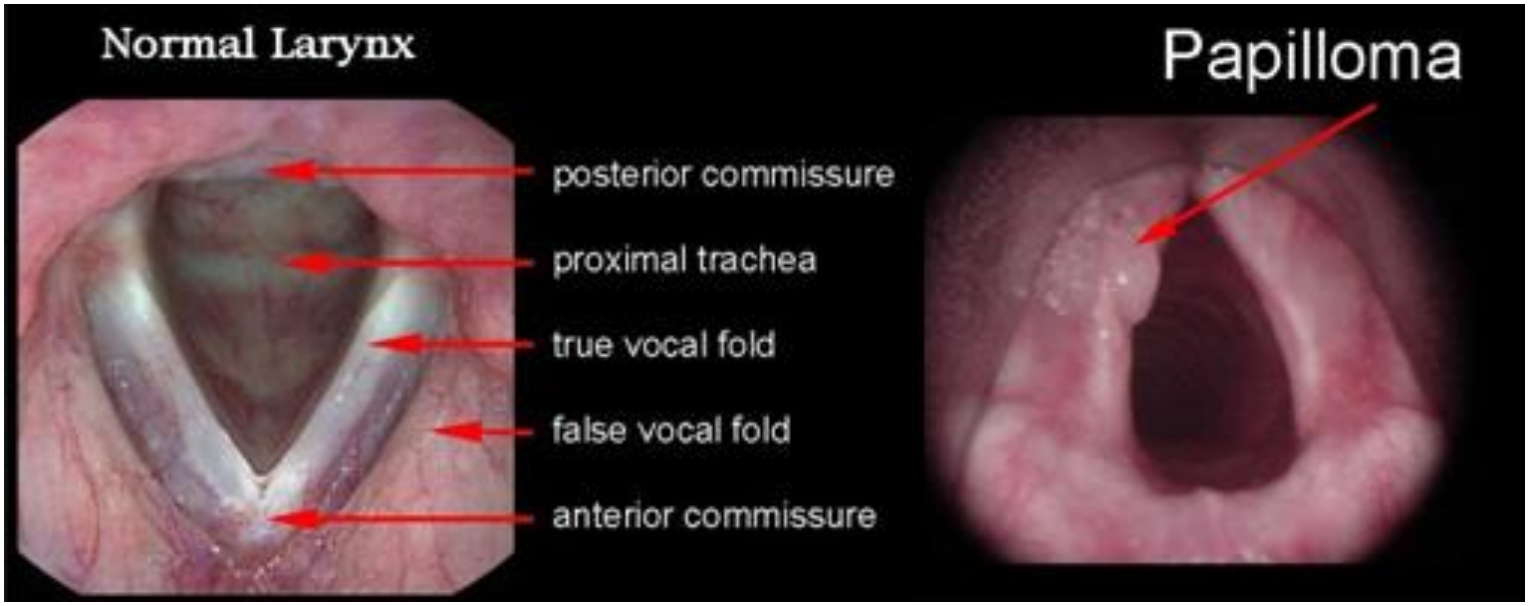
Cancer of the posterior pharyngeal wall

- Advanced at diagnosis (silent).
- Pain, bleeding, weight loss.
- Neck mass is common initial sign.
- 25% T_1 have palpable nodes; >66% T_3, T_4
- Bilateral nodal involvement common.
- Survival >70% stage I, II; 42%, stage III; 27%, stage IV.

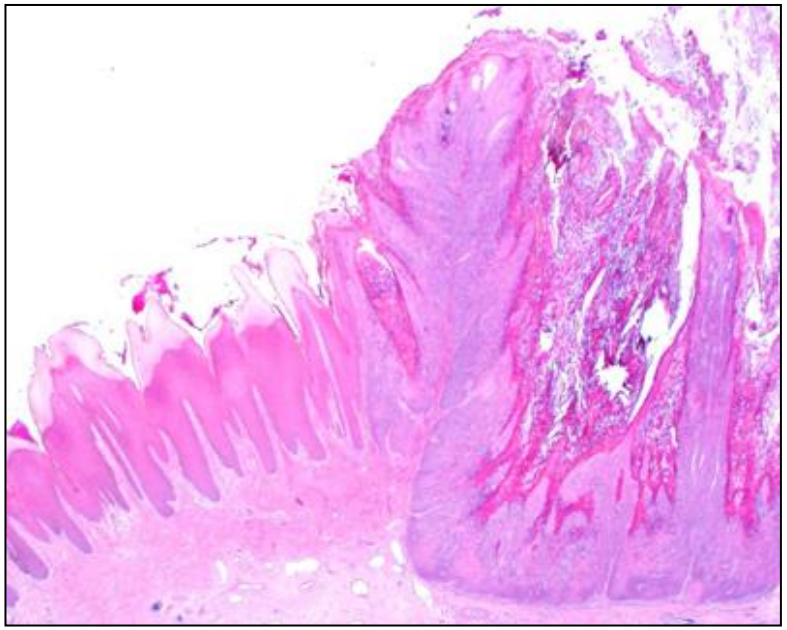
LARYNX

Laryngeal papilloma

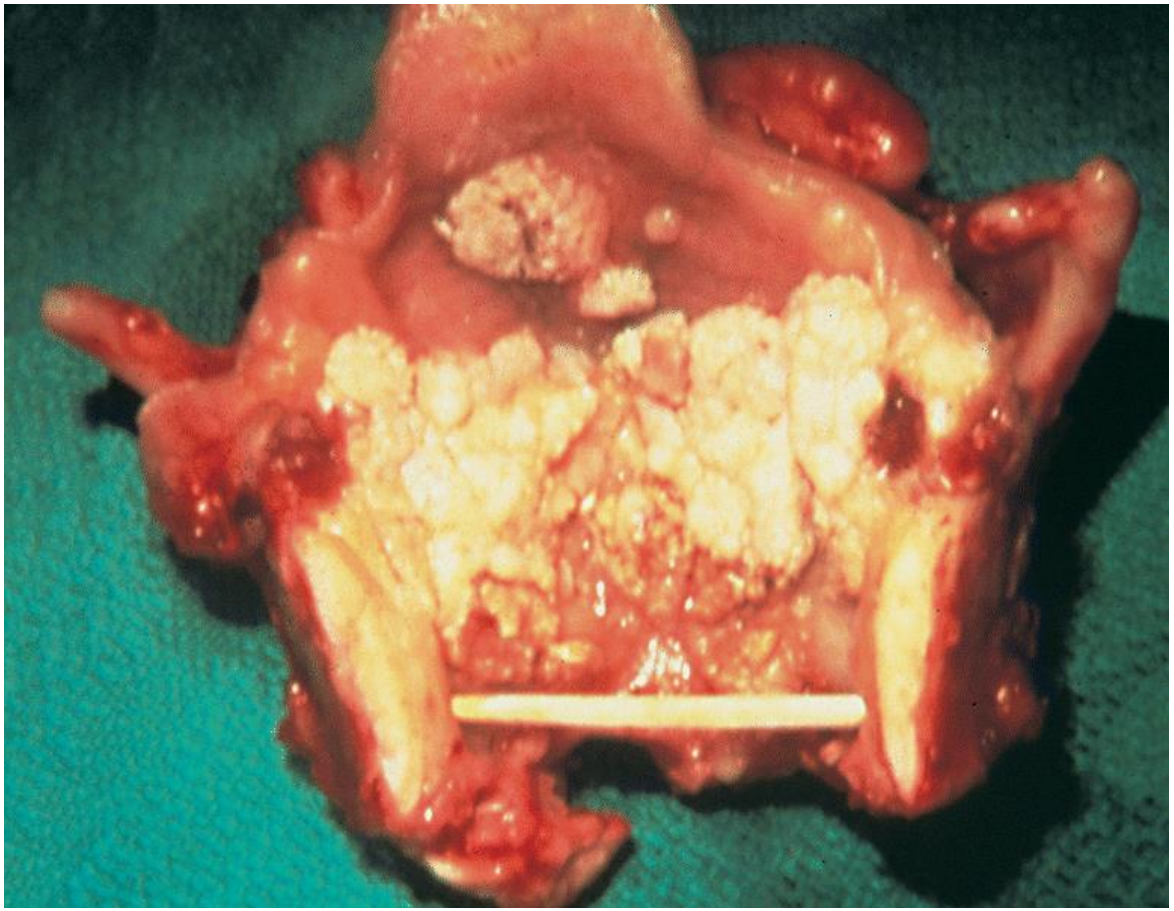
- Papillomas are made up of multiple slender, finger-like projections supported by central fibrovascular cores and covered by an orderly stratified squamous epithelium.
- Single in adults
- Multiple lesions in adults usually caused by HPV 6 and 11
- Juvenile laryngeal papillomatosis generally regresses at puberty



- Laryngeal papilloma
- Finger-like off-shoots of lining epithelium are shown in the microscopic slide (right).
- HPV most common cause



Laryngeal papillomatosis



Gross laryngectomy specimen from a patient with multiple juvenile papillomas showing diffuse involvement of the true vocal cords, and supraglottic and subglottic larynx.

Fig. 3-16

Mills, SE, Gaffey, MJ, Frierson ,HF. , "Tumors of the upper aerodigestive tract and ear." Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Cancer of the larynx

- 95% are squamous cell tumors
- The tumor usually develops on the vocal cords
- Those confined within the larynx proper are termed intrinsic, whereas those that arise or extend outside the larynx are called extrinsic.
- They begin as in situ lesions that later appear as pearly gray, wrinkled plaques on the mucosal surface, ultimately ulcerating and fungating.

Cancer of the larynx

- Most arise in glottis.
- 38% supraglottic.
- Infiltrative pattern.
- Hoarseness common.
- 2/3 have nodal metastases at diagnosis.
- Levels II-IV common.

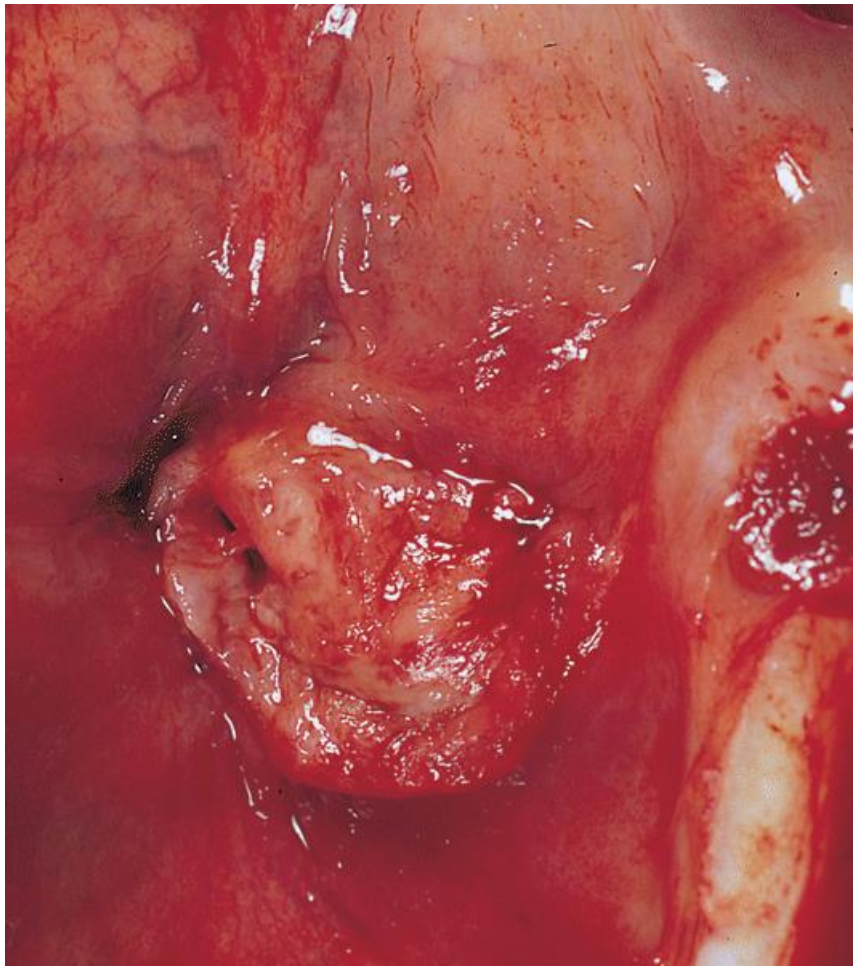
Cancer of the larynx

- 1-8% subglottic lesions
- Infiltrative growth
- Hoarseness rare
- May obstruct airway
- 2/3 have metastases at presentation
- Pretracheal and paratracheal nodes commonly involved.
- 25% survival

Cancer of the larynx

- <2% nodal disease T_1, T_2.
- 25% nodal disease T_3, T_4.
- Survival by depth of invasion:
- >66% T_1, T_2
- 50%, T_3, T_4.
- Survival by stage: 70% stage I
- 50%, stage II, III
- 20%, stage IV.

Squamous carcinoma

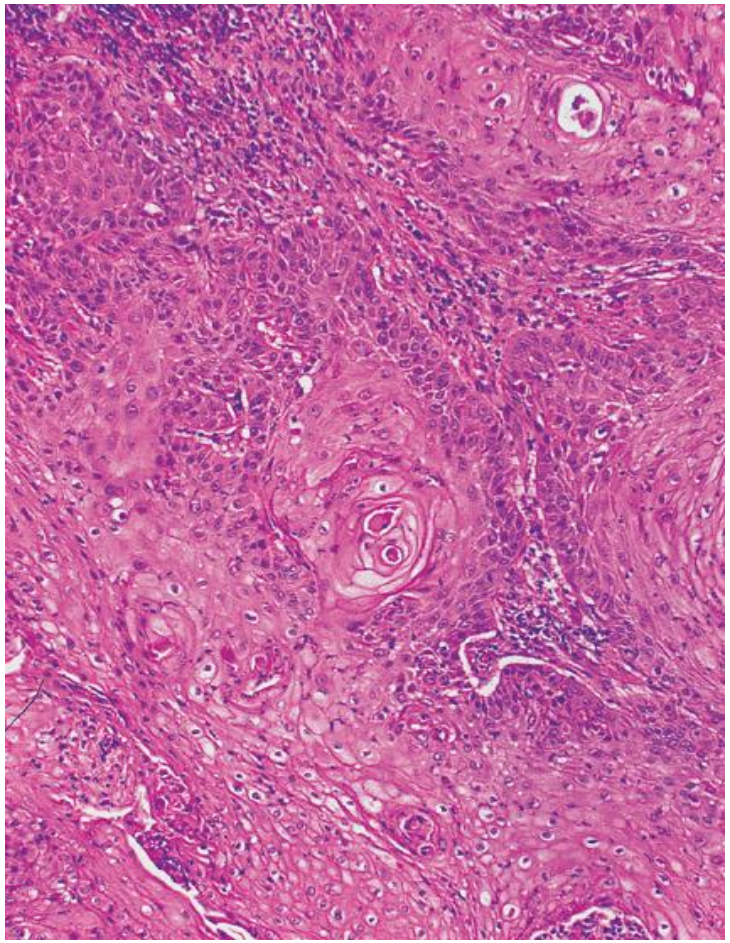


This large squamous cell carcinoma of the right true vocal cord forms a predominantly intraluminal mass. In spite of the size of the lesion, there is no invasion of the ventricle or false cord.

Fig. 4-19

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Squamous carcinoma

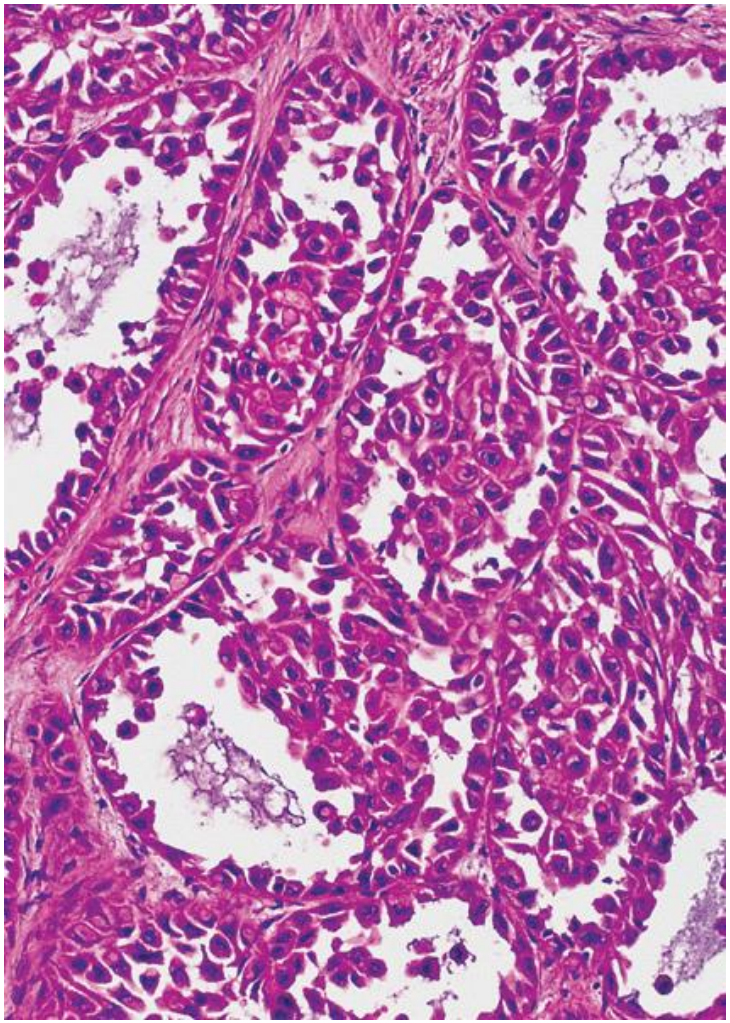


Invasive, well-differentiated squamous cell carcinoma of the larynx consists of large, interconnecting nests of overtly squamous cells. A keratin "pearl" is present in the center of the field.

Fig. 3-10

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

Squamous carcinoma

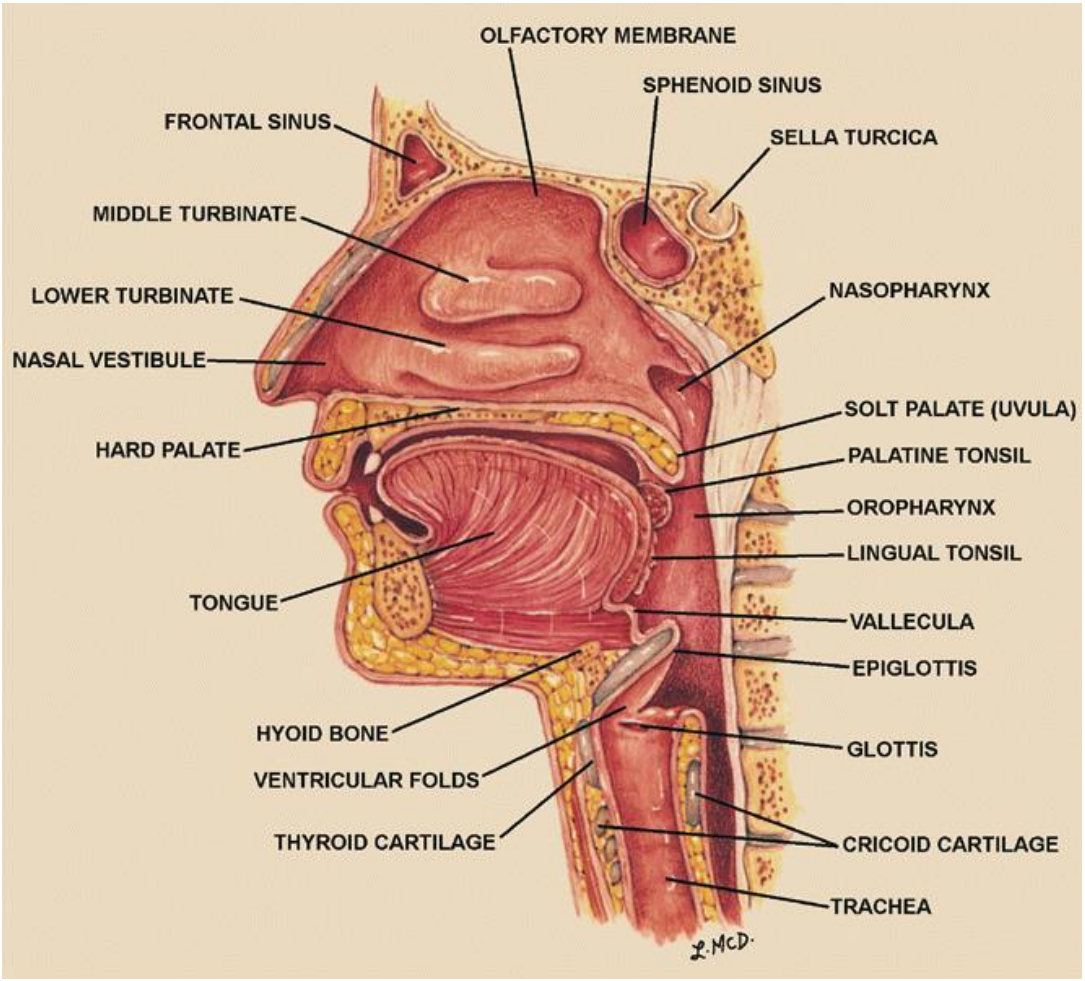


Apparently free- floating nests of squamous cells within the lumens of acantholytic squamous cell carcinoma allow distinction
from adenocarcinoma or angiosarcoma.

Fig. 5-36

Mills, SE, Gaffey, MJ, Frierson, HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Armed Forces Institute of Pathology, Washington, D.C. 2006.

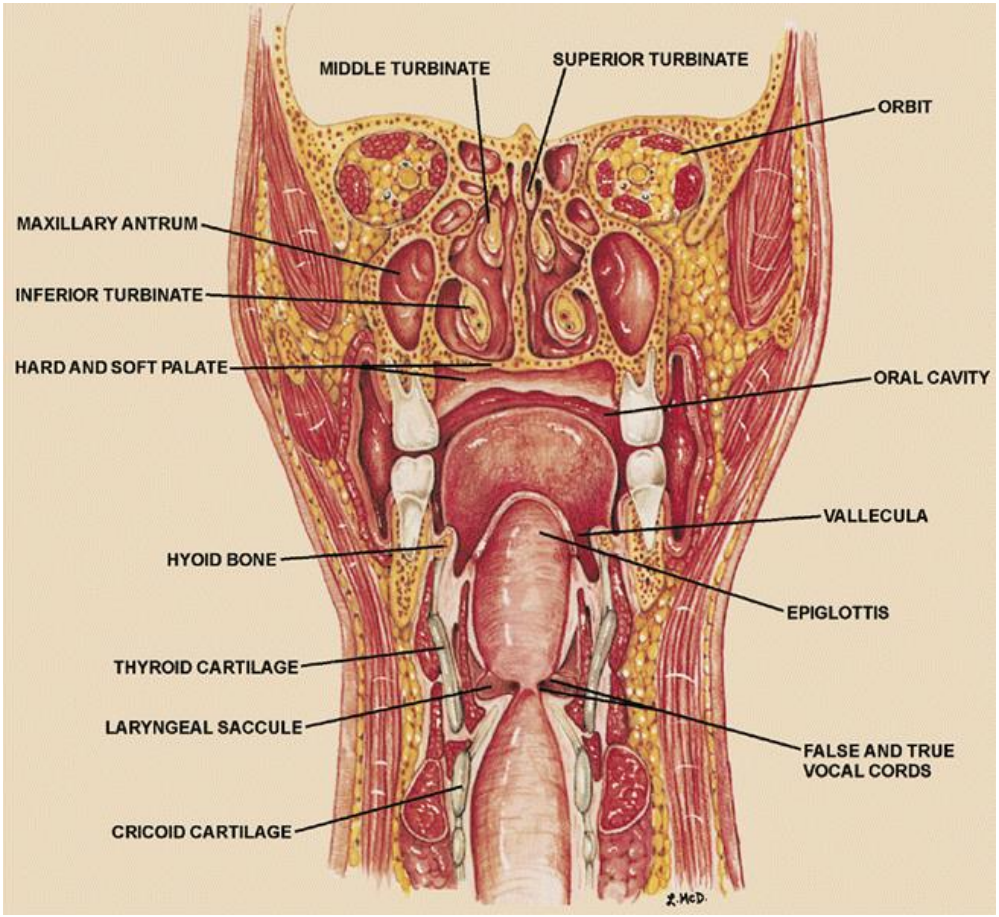
Anatomy



A sagittal section through the head at the level of the molar teeth.

Mills, SE, Gaffey, MJ, Frierson ,HF. , “Tumors of the upper aerodigestive tract and ear.” Atlas of Tumor Pathology, Third Series, Fascicle 26. Fig. 1-1. Armed Forces Institute of Pathology, Washington, D.C. 2006.

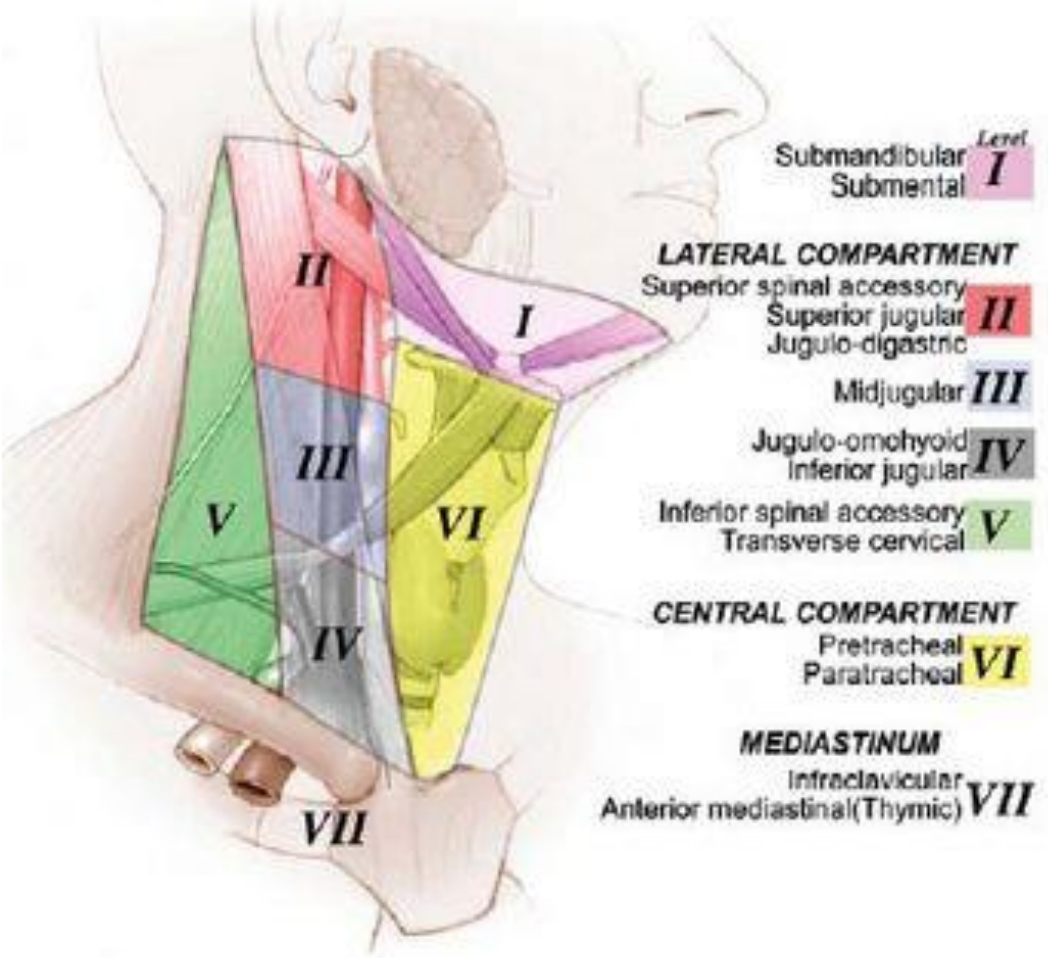
Anatomy



A coronal section through the head at the level of the molar teeth.

Mills, SE, Gaffey, MJ, Frierson ,HF. , "Tumors of the upper aerodigestive tract and ear." Atlas of Tumor Pathology, Third Series, Fascicle 26. Fig. 1-2
Armed Forces Institute of Pathology, Washington, D.C. 2006.

Surgical levels in neck



https://epomedicine.com/medical-students/lymph-node-levels-of-neck/
Accessed 11/22/2019

Lymphatic drainage in head and neck

Lymphatic drainage	Likely primary sites
Level I: Includes the submental and submandibular triangles	
Submental	Lower lip, chin, anterior oral cavity (including anterior one-third of the tongue and floor of the mouth)
Submandibular	Upper and lower lips, oral tongue, floor of the mouth, facial skin
Level II: Includes the superior jugular chain nodes extending from the mandible down to the carotid bifurcation and posterior border of the sternocleidomastoid muscle	Oral cavity and pharynx (including soft palate, base of the tongue, and piriform sinus)
Level III: Consists of the jugular nodes from the carotid bulb inferiorly to the omohyoid muscle	Larynx, hypopharynx, and thyroid
Level IV: Continues from the omohyoid muscle inferiorly to the clavicle	Larynx, hypopharynx, thyroid, cervical esophagus, and trachea
Level V: Represents the posterior border of the sternocleidomastoid anteriorly, the anterior border of the trapezius posteriorly, and the clavicle inferiorly	Nasopharynx, thyroid, paranasal sinuses, and posterior scalp
Supraclavicular	Infraclavicular sites (including lungs, esophagus, breasts, pancreas, gastrointestinal tract, gastrointestinal and genitourinary sources)

https://epomedicine.com/medical-students/lymph-node-levels-of-neck/
Accessed 11/22/2019

Probable source of nodal metastasis

- Level 1: Oral cavity, submandibular gland
- Level 2: Nasopharynx, oropharynx, parotid, supraglottic larynx
- Level 3: Oropharynx, hypopharynx, supraglottic larynx
- Level 4: Subglottic larynx, hypopharynx, esophagus, thyroid
- Level 5: Nasopharynx, oropharynx
- Level 6 & 7: Thyroid, larynx, lung

Level		Lymph nodes	Boundaries
I	A	Submental nodes	Bilaterally: Anterior belly of digastricus Inferiorly: Hyoid bone Superiorly: Mandible Posteroinferiorly: Posterior belly of digastrics Anteroinferiorly: Anterior belly of digastrics
	B	Submandibular nodes	
II	A (Anterior to the vertical line in relation to spinal accessory nerve) B (Posterior to the vertical line in relation to spinal accessory nerve)	Upper internal jugular (deep cervical) nodes	Superiorly: Skull base Inferiorly: Inferior border of hyoid bone and Carotid bifurcation Posteriorly: Posterior border of Sternocleidomastoid (SCM) Anteriorly: Lateral border of Sternohyoid and Stylohyoid

Level	Lymph nodes	Boundaries
III	Mid internal jugular (deep cervical) nodes	Superiorly: Inferior border of hyoid bone and Carotid bifurcation Inferiorly: Inferior border of cricoid cartilage and Junction of omohyoid muscle and IJV Posteriorly: Posterior border of SCM Anteriorly: Lateral border of sternohyoid
IV	Lower internal jugular (deep cervical nodes)	Superiorly: Inferior border of cricoids cartilage and Junction of omohyoid and IJV Inferiorly: Clavicle Posteriorly: Posterior border of SCM Anteriorly: Lateral border of sternohyoid

Level		Lymph nodes	Boundaries
V	A (Above the horizontal plane marking the inferior border of arch of cricoids cartilage) B (Below the horizontal plane marking the inferior border of arch of cricoids cartilage)	Posterior triangle (spinal accessory) nodes	Superiorly: Convergence of SCM and trapezius Inferiorly: Clavicle Posteriorly: Anterior border of trapezius Anteriorly: Posterior border of SCM

Level	Lymph nodes	Boundaries
VI (Prelaryngeal or Delphian, Pretracheal, Paratracheal, Prethyroidal)	Anterior compartment (midline) nodes	Superiorly: Hyoid bone Inferiorly: Suprasternal notch Bilaterally: Carotid arteries
VII	Upper mediastinal nodes	Below suprasternal notch

https://epomedicine.com/medical-students/lymph-node-levels-of-neck/
Accessed 11/22/2019

Therapy

- Laryngo-pharyngectomy and neck dissection has been the most frequently used therapy for hypopharyngeal cancers.
- For those cases of pyriform sinus cancers that arise in the upper lateral wall, a partial laryngo-pharyngectomy may be successfully used to preserve vocal function.
- Post-operative radiation therapy follows to the primary site and to both sides of the neck to include the retropharyngeal and lateral cervical nodes
- Neoadjuvant cisplatin and 5FU permit larynx preservation

Therapy

- Radiation is as efficacious as surgery in early stage laryngeal cancers (T_1, T_2).
- Surgery combined with postoperative radiation is the treatment of choice of locally advanced cancers (T_3,T_4).
- Docetaxel, cisplatin, and infused 5FU is the induction drug regimen of choice for preservation of the larynx in locally advanced disease.
- The induction regimen may be followed by radiation with cisplatin and infusional 5FU chemotherapy or radiation followed by chemotherapy as the latter is associated with fewer complications.

Therapy

- Metronomic chemotherapy refers to the maintenance therapy with low doses of cytotoxic drugs repeatedly delivered over shorter intervals without interruption
- Tegafur-uracil following radiotherapy
- PD-L1 with cisplatin-5FU or without chemotherapy in refractory squamous oral cancer
- PD-L1 (>20 combined positive score; >50 total positive score)
- Pembrolizumab plus cisplatin and 5FU in metastatic or recurrent cancer
- H-RAS >25, tipifarnib therapy

Therapy

- Following high dose radiation, a checkpoint inhibitor is suggested therapy.
- In recurrent or metastatic disease, cisplatin with infused 5FU plus cetuximab is optimal chemotherapy regimen.
- EGFR copy number not predictive of response
- Elective node dissection is often carried out after chemoradiation for N_2 or N_3 disease.

Therapy

- Localized cancers
- Supraglottis
- Standard treatment options:
- External-beam radiation therapy (EBRT) therapy alone.
- Supraglottic laryngectomy.
- Total laryngectomy may be reserved for patients unable to tolerate potential respiratory complications of surgery or the supraglottic laryngectomy.

Therapy

- Localized cancers
- Glottis
- Standard treatment options:
- Radiation therapy
- Endoscopic CO_2 laser excision
- Cordectomy for very carefully selected patients with limited and superficial T1 lesions
- Partial or hemi-laryngectomy or total laryngectomy, depending on anatomic considerations.

Therapy

- Localized lesions
- Subglottis
- Standard treatment options:
- Lesions can be treated successfully by radiation therapy alone with preservation of normal voice.
- Surgery is reserved for failure of radiation therapy or for patients who cannot be easily assessed for radiation therapy.

Therapy

- Advanced cancers
- Supraglottis
- Standard treatment options:
- Concurrent chemoradiation therapy can be considered for patients who would require total laryngectomy for control of disease.
- Neoadjuvant chemotherapy followed by concurrent chemoradiation therapy
- Laryngectomy is reserved for patients with less than a 50% response to chemotherapy or who have persistent disease following radiation

Therapy

- Definitive radiation therapy alone with altered fractionation in patients who are not candidates for concurrent chemotherapy and surgery (total laryngectomy) for salvage of radiation failures.
- Surgery with or without postoperative radiation therapy

Therapy

- Advanced cancers
- Glottis
- Standard treatment options:
- Concurrent chemoradiation therapy can be considered for patients who would require total laryngectomy for control of disease.
- Neoadjuvant chemotherapy followed by chemoradiation.
- Laryngectomy is reserved for patients with less than a 50% response to chemotherapy or who have persistent disease after radiation.

Therapy

- Definitive radiation therapy alone with altered fractionation in patients who are not candidates for concurrent chemotherapy and surgery (total laryngectomy) for salvage of radiation failures.
- Surgery with or without post-operative radiation therapy.

Therapy

- Advanced cancers
- Subglottis
- Standard treatment options:
- Laryngectomy plus isolated thyroidectomy and tracheoesophageal node dissection usually followed by post-operative radiation therapy.
- Treatment by radiation therapy alone is indicated for patients who are not candidates for surgery.
- Patients should be closely followed, and surgical salvage should be planned for recurrences that are local or in the neck.

Therapy

- Definitive radiation therapy alone with altered fractionation in patients who are not candidates for concurrent chemotherapy and surgery (total laryngectomy) for salvage of radiation failures.
- Induction chemotherapy followed by chemoradiation.
- Laryngectomy is reserved for patients with less than a 50% response to chemotherapy or who have persistent disease after radiation.