HPV-Related Oropharyngeal Squamous Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Refers to oropharyngeal squamous cell carcinoma caused by **human papillomavirus** (OPSCCa-HPV)
- Recognized as **distinct subcategory of oropharyngeal SCCa** in 2017 8th edition of American Joint Committee on Cancer (AJCC) Staging Manual with unique TNM staging

IMAGING

- **CECT/MR**
  - Primary tumor: Enhancing mucosal-based mass of palatine tonsil or tongue base
  - Nodal metastases: Ipsilateral level II ± III adenopathy; **commonly cystic**
- PET/CECT useful in cases of occult primary
- **Diagnostic checklist**: Consider metastatic OPSCCa-HPV in adult with new, cystic, lateral mass in upper neck

TOP DIFFERENTIAL DIAGNOSES

- HPV-negative OPSCCa
- Non-Hodgkin lymphoma
- Asymmetric lymphoid tissue
- 2nd branchial cleft cyst

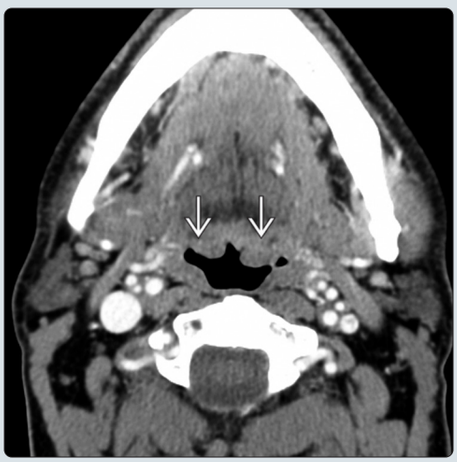
PATHOLOGY

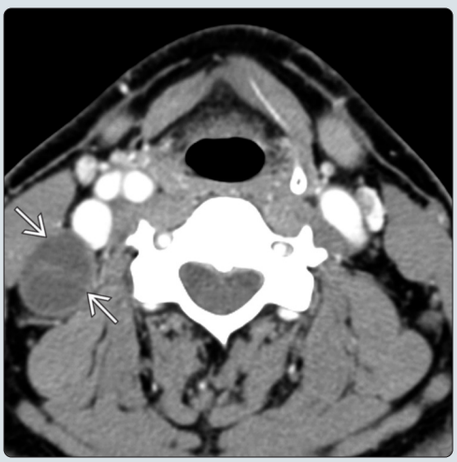
- HPV detected by initially staining for p16 (surrogate marker protein); confirmed by more specific HPV DNA (or RNA) testing
- Tumor cells reminiscent of nonneoplastic tonsillar crypt epithelial cells on routine H&E; keratinization is generally absent or inconspicuous

CLINICAL ISSUES

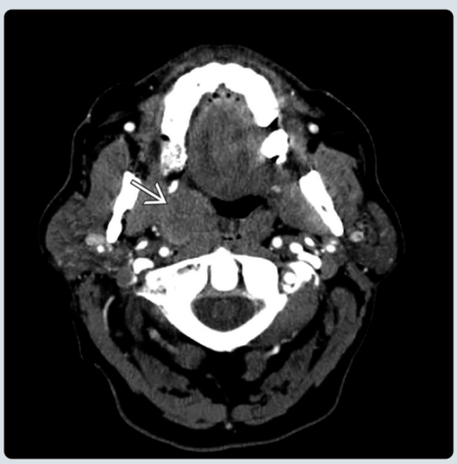
- Presentation: Tonsil/tongue base mass &/or unilateral level II adenopathy in middle-aged man
- Better overall prognosis in general than tobacco-related HPV-negative OPSCC

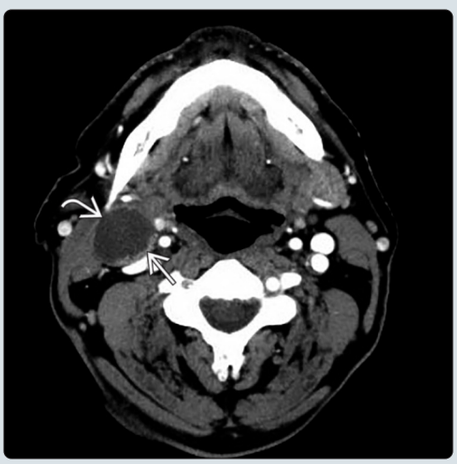
(Left) *Axial CECT shows typical appearance of normal, mildly asymmetric lingual tonsillar tissue ⇨ without a discrete mass.* **(Right)** *Axial CECT (same patient) shows a cystic, septated lymph node in upper right neck ⇨. FNA of node revealed SCCa, and endoscopic biopsy showed primary OPSCCa-HPV in right tongue base. Small tongue base neoplasms may be occult both clinically and on cross-sectional imaging. HPV-positive OPSCC can have small primary tumors but large and often cystic-appearing nodal metastases.*





(Left) *Axial CECT in a 54-year old man with persistent throat pain and development of right-sided swelling below the jaw shows a large right tonsillar mass ⇨.* **(Right)** *Axial CECT through the upper neck in the same patient shows a right cystic level II lymph node ⇨. While there is some minimal wall enhancement posteriorly ⇨, much of the cyst wall is very thin and almost imperceptible in this case of stage I disease for OPSCCa-HPV (T2N1M0).*





TERMINOLOGY

Abbreviations

- Human papillomavirus (HPV)
- Oropharyngeal squamous cell carcinoma (OPSCCa)

Synonyms

- HPV-mediated [p16(+)] oropharyngeal carcinoma

Definitions

- Subcategory of OPSCCa caused by HPV infection
  - Overall better prognosis than conventional SCCa; patients with OPSCCa-HPV may be candidates for less aggressive therapy compared to HPV-negative OPSCCa
- New TNM classification exclusively for HPV-related OPSCCa added in latest 8th edition (2017) of AJCC Cancer Staging Manual

IMAGING

General Features

- Best diagnostic clue
  - Young or middle-aged male nonsmoker with CECT demonstrating enhancing pharyngeal mucosal space (PMS) mass in palatine or lingual tonsil and cystic ipsilateral level II adenopathy

CT Findings

- CECT
  - **Primary mucosal lesion**
    - May be seen as enhancing soft tissue mass in lingual or palatine tonsil; other subsites of oropharynx are less likely
    - Primary lesion may be large and exophytic, protruding into oropharyngeal airway and indistinguishable from HPV-negative carcinoma
    - Primary lesion may be small and occult
  - **Metastatic adenopathy**
    - Oropharynx rich in lymphatics; 70-80% of oropharynx malignancy presents with clinical or radiologic evidence of nodal metastases
    - Pathologic examination of clinical N0 necks reveals 20-30% rate of occult microscopic metastases
    - Morphology of metastatic node ranges from solid → mostly solid → mostly cystic → entirely cystic
    - Although trend toward cystic adenopathy, no particular features can distinguish OPSCCa-HPV nodes from other metastatic disease

MR Findings

- Can be used as primary diagnostic and staging tool; allows for excellent evaluation of primary tumor and nodal drainage pathways
- May provide more detail in cases where CT is limited due to dental amalgam
- T1WI
  - Primary tumor is located in tongue base or tonsil and is isointense to muscle
  - Fat hyperintensity serves as intrinsic contrast to delineate fascial margins
  - Absence of normal fatty striations of tongue musculature may delineate infiltration of tongue base tumor
- T2WI
  - Primary tumor is isointense to slightly hyperintense
  - Metastatic lymph node may be hyperintense to muscle or markedly hyperintense if cystic
- T1WI C+ FS
  - Primary: Enhancing mass in tonsillar bed or tongue base
  - Metastatic nodes enhance homogeneously or heterogeneously if nonnecrotic; peripheral enhancement and central low signal if central necrosis
- DWI
  - Noninvasive prediction of HPV status with good accuracy using ADC and smoking status

Ultrasonographic Findings

- Most commonly identify enlarged solid and cystic nodes level II and III; assessment should include lower neck nodes and bilateral nodes

Nuclear Medicine Findings

- PET/CT
  - HPV-positive OPSCCa primary and nodal metastasis will be FDG avid
  - Highly accurate in detection of primary tumor
  - PET is recommended initial work-up for H&N cancers of unknown origin; best performed prior to endoscopic biopsies

Imaging Recommendations

- Best imaging tool
  - Most common approach CECT with ≤ 3-mm slice thickness; delay image acquisition ~ 90 sec to guarantee mucosal enhancement
  - PET combined with diagnostic CECT of neck may be best overall approach, but PET not always readily accessible

DIFFERENTIAL DIAGNOSIS

HPV-Negative Oropharyngeal SCCa

- Enhancing, mucosal-based mass of tonsil or tongue base will be indistinguishable from OPSCCa-HPV

Non-Hodgkin Lymphoma

- Lymphoma involving palatine or lingual tonsil may present as enhancing, mucosal-based mass
  - OPSCCa usually unilateral, lymphoma often bilateral
  - OPSCCa more common than lymphoma of tonsil
- Cervical lymph nodes with non-Hodgkin lymphoma (NHL) may be indistinguishable from nodal met from OPSCCa

2nd Branchial Cleft Cyst

- Benign, congenital mass usually presents in child or young adult
- Rarely presents for 1st time in adult

Asymmetric Lymphoid Tissue of Pharyngeal Mucosal Space

- Palatine tonsils and lingual lymphoid tissue often asymmetric
- Should have no pathologic adenopathy

HPV-Related Oropharyngeal Squamous Cell Carcinoma

PATHOLOGY

General Features

- **College of American Pathologists (CAP) guidelines** strongly recommend to do high-risk HPV (HR-HPV) testing on all histologic subtypes of newly diagnosed OPSCCa
- Testing performed on primary tumor, or on metastatic regional lymph node if clinical findings consistent with OPSCCa primary
- **HPV testing: p16 kinase inhibitor immunohistochemistry (IHC), or HPV-specific tests for HPV DNA or RNA**
- **p16** kinase inhibitor IHC: CAP-recommended method
  - HPV surrogate marker, sensitive, relatively cheap, easy
  - Moderate to strong intensity block cytoplasmic and nuclear staining in > 70-75% of tumor cells essential for positivity
- HPV-specific tests for DNA or RNA: Commonly used now as confirmatory tests
- Direct test for **HPV DNA:** In situ hybridization (**ISH**) or polymerase chain reaction (**PCR**)
- **RNA ISH**: Newer test to detect HPV E6 and E7 mRNA
  - Best test for overall sensitivity and specificity

Staging, Grading, & Classification

- New TNM classification exclusively for HPV-related OPSCCa introduced in latest 8th edition of AJCC Cancer Staging Manual (2017)
- This staging system is applicable if molecular testing reveals HPV positivity in primary tumor or metastasis
- These cases have **clinical** TNM (cTNM or TNM) staging prior to treatment, and **pathological** TNM (pTNM) classification if surgery is 1st definitive therapy
- cTNM: Using physical examination &/or imaging findings
- pTNM: Clinical staging + surgical and pathology findings
- **T staging**
  - T0 indicates no primary tumor is identified
  - T staging is based on size of primary lesion, measured in greatest dimension with T1 (≤ 2 cm), T2 (> 2 cm but ≤ 4 cm), or T3 (> 4 cm or extension to lingual surface of epiglottis)
  - T4 represents moderately advanced local disease
    - Tumor extends anteriorly into extrinsic musculature of tongue
    - Tumor extends anteriorly from soft palate to hard palate
    - Tumor extends inferiorly into larynx
    - Tumor extends laterally into pterygoid musculature or mandible
    - Tumor extends superiorly to skull base
- **N staging**
  - **Clinical** (including radiologic) staging based on laterality and size of metastatic nodes and **pathologic** staging based on actual number of metastatic nodes
  - Levels II and III most commonly involved; retropharyngeal lymph nodes in ~ 10%
  - NX: Regional lymph nodes cannot be assessed
  - cN0: No regional lymph node involvement
  - cN1: Ipsilateral nodal metastases with no single node > 6 cm
  - cN2: Contralateral or bilateral lymph nodes with no single lymph node > 6 cm
  - cN3: Lymph nodes > 6 cm
  - pN0: No regional lymph node metastases
  - pN1: ≤ 4 metastatic lymph nodes
  - pN2: > 4 metastatic lymph nodes
  - **Extranodal (extracapsular) extension not included** in AJCC 8th edition HPV-positive OPSCC staging
    - Pathologic extracapsular extension may have less prognostic significance in OPSCCa-HPV tumors, but research is ongoing
    - Overt radiographic extracapsular extension can be defined as clear loss of integrity of nodal capsule with infiltration of disease into adjacent fat planes or musculature; may have clinical significance even if no prognostic significance
- **Metastasis staging**
  - cM0: No distant metastasis
  - cM1: Distant metastasis; stage IV reserved for M1 disease
  - pM1: Microscopically confirmed distant metastasis

Gross Pathologic & Surgical Features

- HPV-positive OPSCCa tends to arise from tonsillar crypts, whereas HPV-negative OPSCCa from surface epithelium

CLINICAL ISSUES

Presentation

- Most common signs/symptoms
  - Unilateral mass or adenopathy level II
  - Symptomatic mucosal lesion of oropharynx

Demographics

- Age
  - Younger patient group than HPV-negative OPSCCa
  - Middle aged (31-78 years),White (> 90%), males (85%)

Natural History & Prognosis

- Overall **better prognosis** than patients with oropharyngeal HPV-negative smoking-related OPSCCa

Treatment

- Most often concurrent radiation therapy (XRT) and cisplatin-based chemotherapy
- Transoral robotic surgery (TORS) or transoral laser microsurgery (TLS) ± XRT/chemoXRT

DIAGNOSTIC CHECKLIST

Consider

- OPSCCa-HPV in any adult patient with new, cystic mass in upper neck

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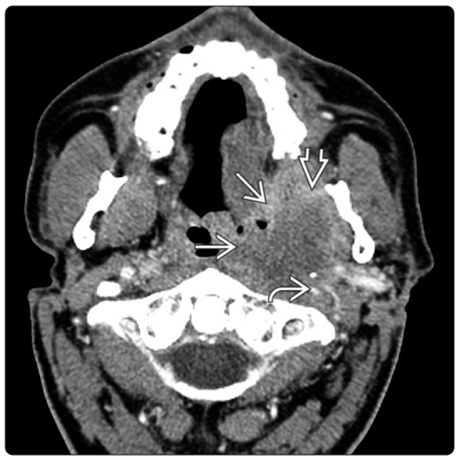
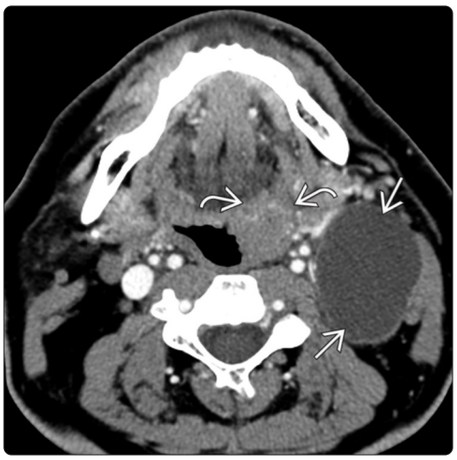
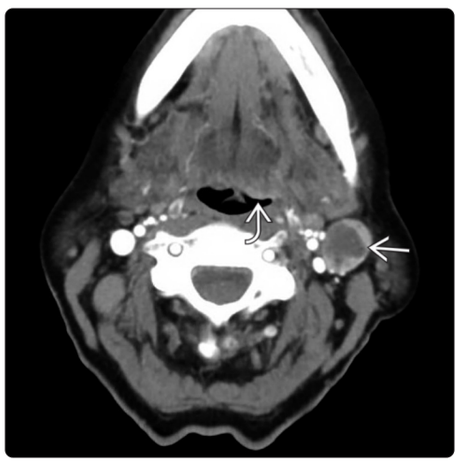
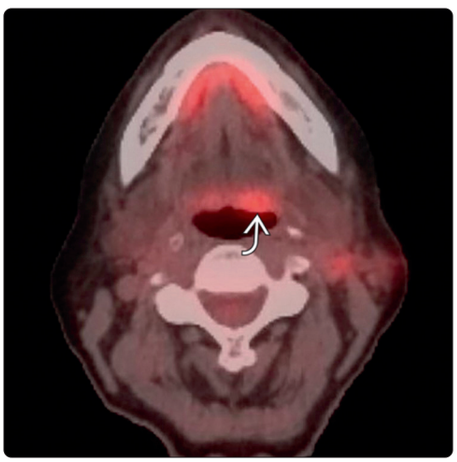


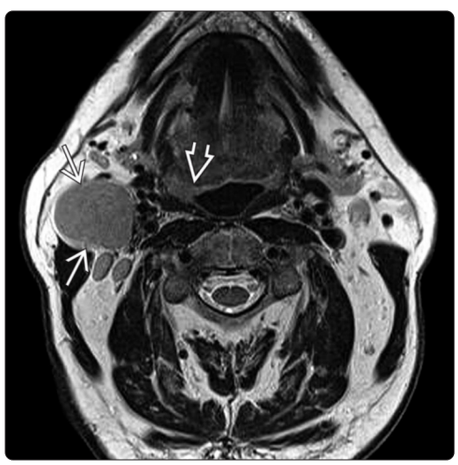


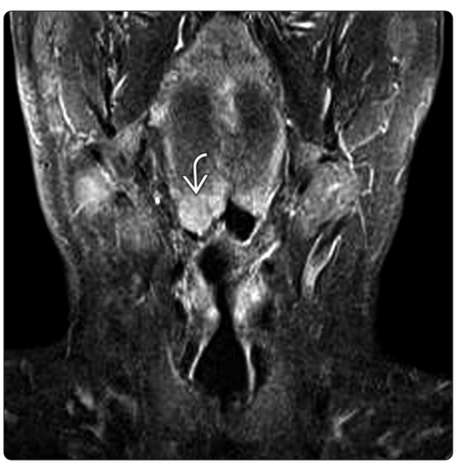
(Left) *Axial CECT shows an advanced T4 stage HPV-positive OPSCC extending into the masticator space and surrounding and narrowing the left internal carotid artery.* **(Right)** *Axial CECT shows a cystic left neck mass mimicking 2nd branchial cleft cyst by location. Note the primary HPV-positive OPSCC in the left palatine tonsil, measuring > 2 cm but < 4 cm, making it a T2 tumor. A cystic neck mass in an adult should be considered as nodal metastasis unless proven otherwise.*





(Left) *Axial CECT in a 64-year-old woman shows an enlarged cystic level II node. Subtle asymmetry of the left tongue base is noted, but no lesion was visible endoscopically.* **(Right)** *Axial PET/CT in the same patient performed after excision of left level II node shows subtle and nonspecific asymmetric increased uptake of the left tongue base. Excisional biopsy revealed OPSCCa-HPV.*





(Left) *Axial T2 MR shows an enlarged, solid, pathologic level IIA node. Subtle asymmetric mucosal thickening of the right tongue base is noted.* **(Right)** *Coronal T2 FS MR in the same patient confirms asymmetry of the right lingual tonsil. Such asymmetry is nonspecific, but ipsilateral adenopathy increases concern for small mucosal lesion. This proved to be HPV-positive OPSCC involving the lingual tonsil.*

IgG4-Related Disease

KEY FACTS

TERMINOLOGY

- Immune-mediated condition associated with fibroinflammatory lesions at nearly any anatomic site
- Historical terms: Küttner tumor (submandibular), Mikulicz syndrome (parotid & submandibular), Riedel thyroiditis
- Nearly any organ system can be involved: Requires clinical, radiologic, serologic, & histopathologic correlation

IMAGING

- Mass-like or diffuse enlargement of involved organ(s)
  - Enhancing, **enlarged salivary glands** on C+ CT/MR
  - T2-hyperintense acutely, hypointense fibrosis chronically
  - Paranasal sinus inflammation ± **CNV enlargement**
- US for often involved major salivary & thyroid glands
  - Hypoechoic nodules &/or reticular pattern
  - High vascularity in nodal & reticular patterns
- CT/MR complementary for deep lesions
- MR for orbit/skull base/intracranial
- F-18 FDG PET useful to assess disease activity

TOP DIFFERENTIAL DIAGNOSES

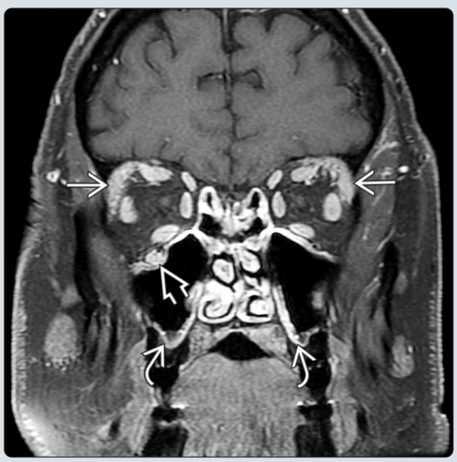
- Sjögren syndrome, parotid
- Non-Hodgkin lymphoma, parotid
- Idiopathic orbital inflammation (pseudotumor)
- Lymphoproliferative lesions, orbit
- Thyroiditis, chronic lymphocytic (Hashimoto)

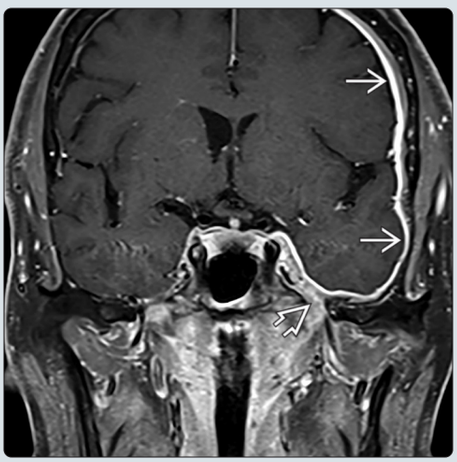
PATHOLOGY

- Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, & IgG4(+) plasma cell infiltrate
- Consider in patients with ↑ serum IgG4 level

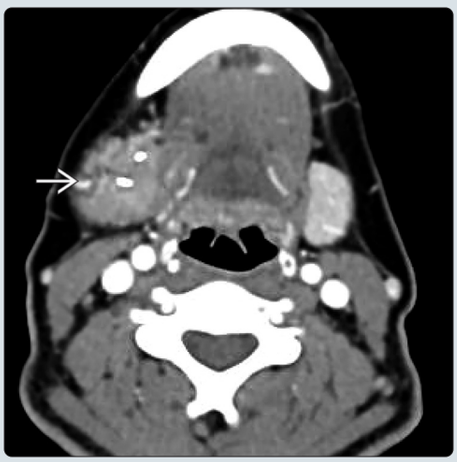
CLINICAL ISSUES

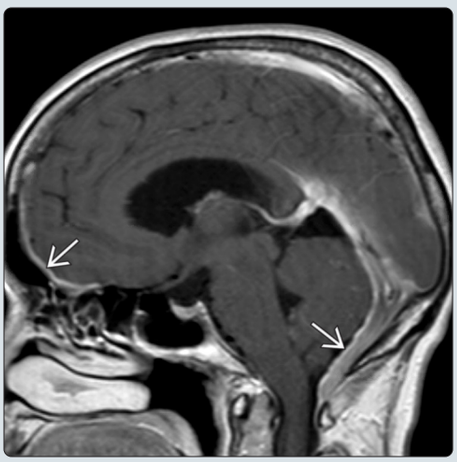
- Multifocal or systemic involvement in 31-62% of cases
- Age 50-70 years in most cases
- Most commonly affected sites: **Pancreatobiliary system > salivary glands & orbits**; each comprise ~ 25% of all cases
- Treatment: Glucocorticoids &/or rituximab
- Consider IgG4-RD with sialadenitis & enlarged CNV





(Left) *Coronal T1 C+ FS MR demonstrates enlarged, enhancing lacrimal glands. Bilateral salivary involvement is most typical, suggesting a systemic etiology. Associated findings of paranasal sinus mucosal thickening and enlarged enhancing infraorbital nerve support IgG4-RD. Patient improved on rituximab.* **(Right)** *Coronal T1 C+ FS MR shows diffuse pachymeningeal thickening and enhancement due to IgG4-RD. There is expansion of the foramen ovale with enhancement along V3, a typical finding.*





(Left) *Axial CECT shows abnormal enlargement of the right submandibular gland with calcifications. The historical term for this was Küttner tumor. While the left submandibular gland appears normal in size, it is abnormally dense/enhancing, as expected for a systemic inflammatory process.* **(Right)** *Midline sagittal T1 C+ MR in a woman with headaches and a history of aortitis shows multifocal pachymeningeal thickening and enhancement. Dural biopsy confirmed dense lymphoplasmacytic infiltrates with increased IgG4.*

TERMINOLOGY

Abbreviations

- IgG4-related disease (IgG4-RD)

Synonyms

- Historical terms in various locations include Küttner tumor (submandibular gland), Mikuliçz syndrome (parotid & submandibular), Riedel thyroiditis
- Orbit involvement previously grouped with nonspecific idiopathic orbital inflammation [(IOI), a.k.a. pseudotumor] but now recognized as separate entity
- Skull base "pseudotumor" can be due to IgG4-RD

Definitions

- Systemic immune-mediated disease with fibroinflammatory lesions at nearly any anatomic site (likely autoimmune)
- Requires clinical, radiologic, serologic, & histopathologic correlation; immunohistochemistry has improved characterization of this disease

IMAGING

General Features

- Best diagnostic clue
  - Dependent on organ involved
  - Glandular involvement usually diffusely involved with fibroinflammatory change
- Location
  - Endocrine & exocrine glands most common but may involve any organ
    - Typical head & neck sites include **major salivary glands**, orbits, meninges, pituitary & thyroid gland
    - Sites outside head and neck/CNS: Pancreas, biliary tree, retroperitoneum, aorta, lungs, kidneys
  - Major salivary glands
    - Glands enlarge acutely
    - Findings may mimic Sjögren syndrome
    - Small, T2-hyperintense micronodules
  - Orbit & lacrimal glands
    - Lacrimal gland enlargement (mimics lymphoma)
    - Trigeminal nerve enlargement & enhancement (especially V2)
    - Look for adjacent pan-sinus mucosal thickening
    - Bilateral involvement strongly associated (~ 80%) with extraophthalmic manifestations (neck, chest, abdominal & pelvic CECT useful to screen)
    - Extraocular muscle enlargement or orbital fat involved less frequently
  - Thyroid
    - Enlarged glands with micronodularity
    - US is more sensitive than CT/MR
    - Findings overlap with chronic lymphocytic (Hashimoto) thyroiditis (fibrosing subtype)
  - Lymph nodes
    - Adenopathy is typically nonspecific on imaging
  - Pachymeninges
    - Thickened & enhancing
    - May have cranial nerve involvement, especially enlarged CNV
    - Pituitary infundibulum thickening & enhancement due to hypophysitis
  - Paranasal sinuses
    - May appear similar to sinusitis or can be mass-like with bone destruction
  - Involvement outside CNS + head & neck
    - Most common is pancreatic (imaging shows "sausage" pancreas with peripheral edema halo)
- Size
  - Variable; often entire gland/organ involved due to systemic nature
- Morphology
  - Linear fibrosis & microcystic changes most often

Radiographic Findings

- IGg4-RD often causes masses that mimic neoplasms, hence historical references to "tumor" or "pseudotumor" in many locations
  - Pseudotumor in orbital inflammation
  - Küttner tumor in submandibular gland
  - Skull base pseudotumor
- Glandular characterization best seen with US > MR/CT

CT Findings

- Orbit and lacrimal glands
  - Lesions with regular borders
  - Multiple lesions, especially bilateral lacrimal gland enlargement
  - Higher median postcontrast CT Hounsfield unit (HU) values & postcontrast/precontrast CT:HU ratios compared to orbital lymphoma
  - Extraocular muscle enlargement (predilection for superior & inferior rectus muscles)
  - Adjacent paranasal sinus mucosal thickening
- **PET/CT**
  - Areas of active involvement are hypermetabolic
  - F-18 FDG PET useful to assess disease activity

MR Findings

- T1WI
  - Lesions are hypointense
- T2WI
  - Usually iso- to hypointense due to fibrosis
- T1WI C+
  - Areas of involvement show enhancement
- Uncommon locations
  - Pituitary infundibulum thickening & enhancement due to hypophysitis
  - Association with other autoimmune diseases

Ultrasonographic Findings

- Grayscale ultrasound
  - Hypoechoic nodules &/or hyperechoic lines & spots with reticular pattern
  - Submandibular > parotid gland involvement
- Color Doppler
  - High vascularity in nodal & reticular patterns

Imaging Recommendations

- Best imaging tool
  - US for major salivary & thyroid glands
    - May guide fine-needle aspiration (FNA) or biopsy to establish diagnosis
  - MR for orbit/skull base/intracranial

- Protocol advice
  - US for salivary & thyroid gland through cross-sectional imaging complementary
  - CT or MR for deep lesions & CNV involvement
  - MR for orbits & brain

DIFFERENTIAL DIAGNOSIS

Sjögren Syndrome, Parotid

- Small cysts &/or nodules ± punctate calcifications
- Anti-SSA & SSB antibodies

Non-Hodgkin Lymphoma, Parotid

- Parotid soft tissue mass ± adenopathy
- Enlarging mass requires histologic sampling

Idiopathic Orbital Inflammation (Pseudotumor)

- Pain, erythema, proptosis, & restricted ocular motility
- More often unilateral than IgG4-RD

Lymphoproliferative Lesions, Orbit

- Lacrimal gland enlargement mimics IgG4-RD
- CNV involvement ± paranasal sinus inflammation unlikely
- Likely will require biopsy to differentiate

Thyroiditis, Chronic Lymphocytic (Hashimoto)

- Requires biopsy differentiation
- Thyroiditis, invasive fibrous, subtype (Riedel) now recognized as IgG4-RD

PATHOLOGY

General Features

- IgG4:IgG(+):plasma cell ratio of > 40% suggests Küttner tumor (IgG4-RD)
- Consider in patients with ↑ serum IgG4 level
- Flow cytometry important to exclude lymphoma

Staging, Grading, & Classification

- American College of Rheumatology/European League Against Rheumatism (EULAR) 3-step criteria for diagnosis
  - ≥ 1 of 11 possible organs involved in manner consistent with IgG4-RD
  - Inclusion criteria from 8 weighted categories of clinical, serologic, radiologic, & pathologic findings
  - Exclusion criteria from 32 clinical, serologic, radiologic, & pathologic items (if any positive, eliminates IgG4-RD)

Gross Pathologic & Surgical Features

- Tumor-like mass or enlargement of 1 or more organ(s)

Microscopic Features

- Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis (least common but most specific), & IgG4+ plasma cell infiltrate

CLINICAL ISSUES

Presentation

- Most common signs/symptoms
  - Multifocal or systemic involvement is typical; seen in 31-62%
  - Age 50-70 years in most cases; uncommon in children
  - M:F = 1.6:1 for head & neck manifestations
    - 4:1 for other sites of organ involvement
  - Dependent on location
    - Major salivary glands: Gland enlargement
    - Thyroid gland: Painless thyroid enlargement
    - Orbit: Proptosis, orbital pain
    - Skull base/pachymeninges: Headache & cranial neuropathies
  - Most commonly affected sites: **Pancreatobiliary > salivary glands > orbit**; each comprise ~ 25% of all cases
    - Orbit & salivary involvement (dacryoadenitis) more common in women
    - Pancreatobiliary involvement more common in men
- Other signs/symptoms
  - Elevated serum IgG4 in 55-97%
    - Especially Asian patients
    - Correlates with number of organs involved
  - Other presenting systemic signs & symptoms are infrequent
  - Weakness or weight loss; each reported in ~ 25% of cases

Demographics

- Middle-aged adults

Natural History & Prognosis

- Variable but usually treatment-responsive; however, may cause organ failure & even death if unrecognized
- Limited head & neck or retroperitoneal involvement are more treatment-resistant than pancreatobiliary & systemic

Treatment

- Responds to glucocorticoids &/or rituximab
- Disease-modifying antirheumatic drugs

Complications

- ↑ risk for malignancy
- ↑ risk for intracerebral aneurysms

DIAGNOSTIC CHECKLIST

Consider

- Tissue sampling to exclude lymphoma if enlarging mass

Image Interpretation Pearls

- Consider IgG4-RD with sialadenitis ± dacryoadenitis & enlarged CNV

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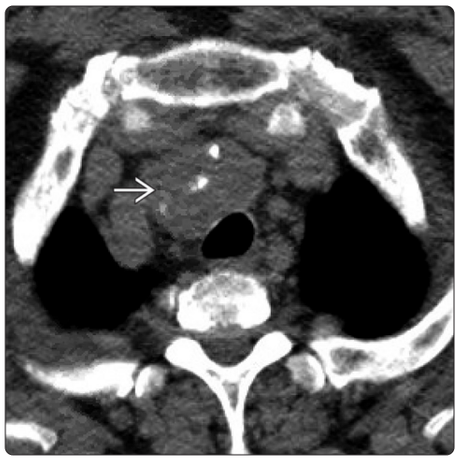
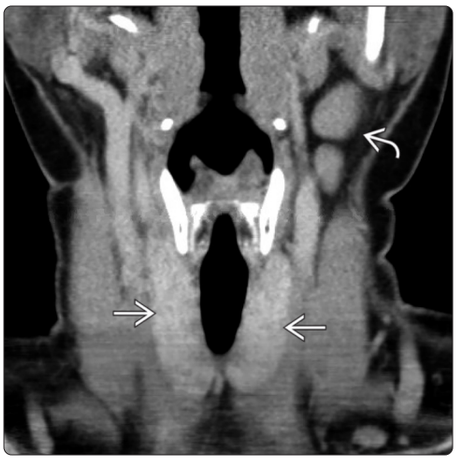
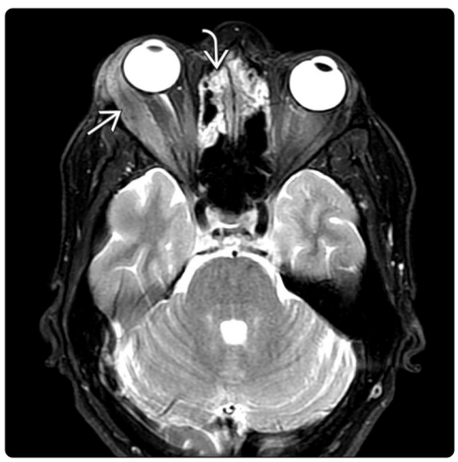
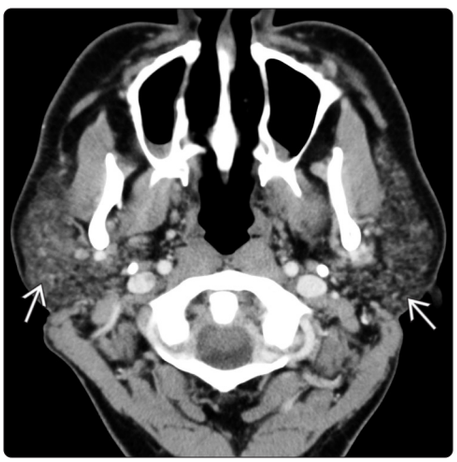


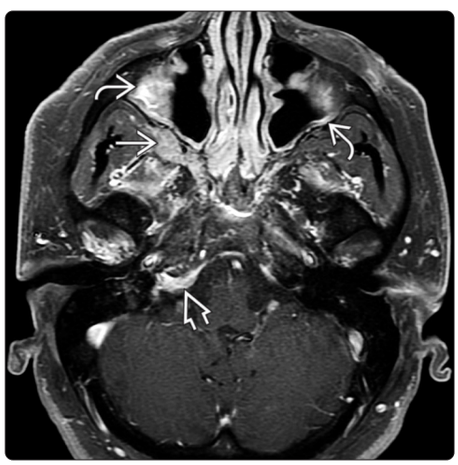


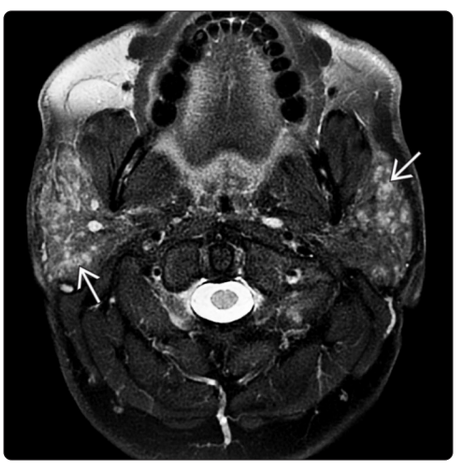
(Left) *Axial NECT shows thyroid gland enlargement with coarse calcifications. Although not specific, this patient had IgG4-RD involving the thyroid. Historically, this has been labeled as Riedel thyroiditis.* **(Right)** *Coronal CECT MPR demonstrates subtle enlargement of thyroid gland with tiny, granular hypodensities. Findings are more evident on US but overlap with chronic lymphocytic thyroiditis. Associated nonspecific-appearing involved level II lymph nodes are noted. Biopsy confirmed IgG4-RD.*





(Left) *Axial T2 FS MR shows an enlarged, hyperintense lacrimal gland due to IgG4-RD. Asymmetric involvement like this is less common and more challenging diagnostically. Associated paranasal sinus mucosal thickening is noted, a common associated finding.* **(Right)** *Axial CECT in the same patient demonstrates bilateral parotid enlargement with diffuse micronodularity of the parenchyma. Findings are similar to Sjögren but lack the cystic changes typical of acute involvement. Findings were due to IgG4-RD.*





(Left) *Axial T1 C+ FS MR show focal soft tissue thickening and enhancement within the pterygopalatine fossa along V2 due to confirmed IgG4-RD. Paranasal sinus inflammation is noted. Focal pachymeningeal thickening and enhancement, although not specific, can also be seen with IgG4-RD. Note also dural involvement.* **(Right)** *Axial T2 FS MR in the same patient shows bilateral parotid gland enlargement with multiple small, nodular foci of hyperintensity. Findings improved after treatment with rituximab.*

Introduction

Squamous cell carcinoma (SCCa) is the most common malignancy in the head and neck (H&N). Recent developments in the understanding of the molecular nature and causes of SCCa now reveal it to be a heterogeneous malignancy.

In most sites of the H&N, **tobacco** is the most common causative agent of mucosal dysplasia and neoplasia. **Alcohol** is a synergistic cofactor, while poor oral hygiene and genetics are also contributing risk factors. Paralleling the declining trend of smoking over the last few decades, there has been an overall decline in the incidence of H&N SCCa, particularly in the oral cavity, larynx, and hypopharynx.

Conversely, in the oropharynx, there has been a rise in **base of tongue [(BOT)/lingual tonsil)]** and **palatine tonsillar SCCa**, particularly in middle-aged (31-78 years) White (> 90%) males (85%) who may have limited or no history of tobacco and alcohol use. This group of **oropharyngeal SCCa (OPSCCa)** tumors is positive for **human papillomavirus (HPV)**, most commonly HPV-16 subtype, which is also responsible for anogenital neoplasms. The past few decades have seen a 225% increase in HPV(+) OPSCCa, and a 50% reduction in HPV(-) OPSCCa. Currently, 80% of OPSCCa in the USA are HPV related with risk directly correlating to number of sexual partners and oral sex practices. HPV(+) OPSCCa is more responsive to chemoradiation than HPV(-) OPSCCa, and patients have an overall better survival rate. Patients who are smokers with HPV(+) tumors carry an intermediate prognosis. A new TNM classification has been added exclusively for HPV(+) OPSCCa in the current (**8th ed.**) American Joint Committee on Cancer (AJCC) staging manual. Previously, AJCC TNM staging was the same for all OPSCCa. **Extranodal extension (ENE)** of metastatic disease in lymph nodes is a high-risk, poor prognostic factor for most H&N tumors, but ENE is not included in AJCC 8th ed. nasopharyngeal carcinoma (NPCa) and HPV(+) OPSCCa staging, as pathologic data suggest that perinodal inflammatory changes may simulate ENE in viral-related cancers.

NPCa is a distinctly different neoplasm with the most common histopathologic subtypes associated with **Epstein-Barr virus (EBV)** infection. The least common and most aggressive form (keratinizing NPCa) is related to tobacco and alcohol abuse, although some pathology literature has also suggested an association with HPV infection. **SCCa of the larynx** is strongly associated with tobacco and alcohol abuse, especially in males > 50 years of age. But, recently there is increasing incidence of HPV-related laryngeal cancer cases in younger, < 30-year-old nonsmokers, which is higher in females than males. However, the **College of American Pathologists (CAP) guidelines** suggest not to routinely perform high-risk-HPV testing on oropharyngeal non-SCCas (CAP expert consensus opinion) or on nonoropharyngeal primary tumors of H&N (CAP recommendation). This is due to the fact that HPV positivity does not really affect aggressiveness or prognosis/therapeutic difference in these tumors.

While our current understanding of SCCa is evolving through greater molecular interrogation of these tumors, the radiologist's roles remain largely unchanged. At the time of diagnosis, the radiologist must report details about the primary tumor to assign a **tumor stage**, including **size** and **local extent** of the primary, detecting perineural tumor (**PNT**) spread, and assessing regional **nodes** and **distant** spread of disease. Following treatment, both **baseline** and **surveillance** imaging require careful evaluation to detect **residual** or **recurrent SCCa, treatment complications**, and **2nd primary neoplasms**.

Imaging Approaches & Indications

There is no definitive best imaging modality for all H&N sites when staging SCCa. Some specific tumor sites are better served by either **CECT or MR or PET/CECT**. A patient with copious secretions or pain may not tolerate long MR sequences, and, in that instance, CECT or PET combined with CECT is preferred. Excellent-quality neck imaging is more readily reproducible from patient to patient using CT than MR. Also, large FOV, nonoptimized MR sequences, and lack of familiarity with basic neck anatomy make detection of key findings difficult. A poorly performed, inaccurately reported neck MR is an expensive, unsatisfactory alternative to CT.

MR does offer specific utility in certain areas. e.g., it is the preferred staging tool for **NPCa** because detection of **skull base** infiltration (T3) or **intracranial/cranial nerve** disease (T4) is extremely important for staging and treatment planning. MR offers better soft tissue contrast for detecting small primary tonsillar tumors and evaluating the **deep extent** of a lesion when planning surgical resection or intensity-modulated radiation therapy (IMRT). For this reason, MR may be used in the **oral cavity and oropharynx**. In the **larynx**, MR is so affected by motion artifact that it is largely reserved for determination of **cartilage penetration** (T4a) when CECT is equivocal. **Diffusion restriction**, and **dynamic contrast MR** time-signal intensity curves (**TIC**) showing **early enhancement** with a peak time < 150 s and a **low washout ratio** of < 30% may be seen in malignant tumors. After successful treatment, TIC changes from pretreatment rapid rise and washout to posttreatment slow rise and gradual trapping (wash-in) pattern. Lymph node metastasis at any site is almost equally well evaluated with either CECT or MR, but PET is superior to both with the potential to identify FDG-avid metastasis in normal-sized nodes.

Given the complexity of neck anatomy, **FDG PET** in the H&N is best performed as a combined PET/CECT examination. There are variable degrees of normal FDG uptake in muscles, brown fat, salivary and lymphoid tissue, and recent biopsy sites. These all are potential false-positive pitfalls in PET imaging, but routine measurement and reporting of standardized uptake values can obviate the pitfalls. A potential false-negative finding is absence of FDG uptake in a cystic/necrotic node, but correlation with neck CECT imaging will allow correct identification of cystic/necrotic nodal metastases.

Ultrasound (US) can be helpful in identifying early subcapsular deposits in normal-sized nodes, and ENE of nodal metastasis. US can also serve as imaging guidance for fine-needle aspiration.

Imaging Anatomy

SCCa arises from the mucosal surface of the upper airway and digestive tract, pharynx, and larynx. The pharynx is really a muscular tube encased by the middle layer of deep cervical fascia (DCF) and attached to the skull base by pharyngobasilar fascia. The **pharyngeal mucosal space** is a continuous sheet of tissue on the airway side of the DCF. It is divided into separate sites anatomically. Staging of mucosal SCCa is individualized to each site or subsite.

The **nasopharynx**, posterior to the nasal cavity, extends from the most cranial pharynx at the skull base to the soft palate.

Inferiorly, it is contiguous with the **oropharynx**, which extends caudally to the hyoid bone. Anterior tonsillar pillars and circumvallate papillae of the tongue define the anterior limit of the oropharynx. The anterior 2/3 of the tongue lies in the oral cavity and is known as the oral tongue. The posterior 1/3 is called the tongue base and is part of the oropharynx.

Below the hyoid bone, the pharynx divides to form the larynx, which is continuous with the trachea, and hypopharynx, which joins the cervical esophagus. The **hypopharynx** consists of **3 subsites** starting with the letter "**P**." The posterior wall of the **hypopharynx** (gives rise to 15% of hypopharyngeal SCCa) is a continuation of the posterior wall of the oropharynx. Lateral "pockets" of the hypopharynx form the **p**yriform sinuses and are separated from the larynx by the aryepiglottic (AE) folds. Nearly 65% of hypopharyngeal SCCa arise in the pyriform sinuses. The 3rd subsite of the hypopharynx is the **p**ostcricoid region (20% of hypopharyngeal SCCa). The **larynx** is anterior in the neck and also has **3 subsites**: **Supraglottic** larynx, which includes the epiglottis, AE folds, and false cords; **glottis** with true vocal cords; and **subglottis**, which is contiguous with the cervical trachea. Around 60% of laryngeal SCCa are glottic.

Approaches to Imaging Issues in H&N SCCa

Staging a SCCa is performed using the **AJCC** 8th ed. Referral to the site-specific tumor (T) and nodal (N) features greatly enhances an imaging report. When the size of a T or N is important for tumor or nodal stage, respectively, the **greatest dimension** is measured. Some superficial oral cavity tumors are best measured on clinical examination. The **puffed-cheek** technique, in which the patient purses the lips and puffs out the cheeks, can be extremely helpful to detect small oral cavity tumors and evaluate the surfaces of larger tumors outlined by more air separating normal structures in the oral cavity. This can be easily done in CT, which is acquired in a few seconds, but may be more difficult in MR as the patient will have to do the maneuver for a few minutes during the MR sequence acquisition without moving. The key role of cross-sectional imaging is to evaluate features that are not evident on exam, such as deep extent or bone infiltration, which may upstage a tumor or alter treatment options.

Depth of invasion (DOI) was recently introduced into the oral cavity squamous cell carcinoma (OSCCa) clinical T staging (using clinical examination and imaging) in addition to pathologic T staging in AJCC 8th ed., recognizing its prognostic significance and clinical relevance. DOI is measured from the normal mucosal basement membrane adjacent to the tumor to the deepest point of tumor invasion. This is different from tumor thickness (TT), which measures the distance from the tumor surface to the deepest point of invasion. DOI and TT are the same for flat tumors, as the interpreted normal mucosal basement membrane plane is at the same level as the tumor surface. DOI is smaller than TT in exophytic/bulging tumors that extend outward from the interpreted mucosal plane. DOI is larger than TT in endophytic/ulcerated tumors that have a gap between the interpreted mucosal plane and the tumor surface. e.g., practically in tongue SCCa (any flat, exophytic/bulging or endophytic/ulcerated tumor) DOI is measured perpendicular to a "plumb line" along the lateral border of the tongue. In axial CT/MR, the "plumb line" connects normal tongue tissue anterior and posterior to the tumor along the tongue lateral border. In coronal CT/MR, the "plumb line" connects the normal lateral border tongue tissue superior and inferior to the tumor. In contrast, TT outer measurement is along the aforementioned "plumb line" in flat tumor, lateral to the line in exophytic/bulging tumor, and medial to the line in endophytic/ulcerated tumor. Pathologic DOI measurement uses adjacent normal mucosal basement membrane as the originating point, but the basement membrane is invisible on imaging, as the thickness of the oral mucosal epithelium is just 0.5 mm. The difference between the potential originating points of measurement from the mucosal surface on CT/MR and from the normal basement membrane on surgical specimen is negligible. There is a high radiologic and pathologic TT correlation (0.78) in all oral cavity subsite tumors. Pathologic TT (pTT) on a surgical specimen is slightly thinner than radiologic TT (rTT) on CT/MR, apparently due to tumor shrinkage on formaldehyde fixation of the surgical specimen. The shrinkage factor is smaller for the oral tongue (0.91) compared to other oral cavity subsite tumors (0.70), thought to be due to more free margins in the tongue leading to less propensity to shrink, than other subsite tumors more deeply embedded in tissues. rTT-pTT correlation is suboptimal when there is > 8 weeks to surgery after imaging, as the tumor would have grown in between. rTT on MR has a slightly higher correlation with pTT in comparison to rTT on CT, but the difference is not statistically significant. As most OSCCa are flat tumors (88%), TT is the same as DOI in most, and both of these are independent predictors of survival, which can stratify death risk in addition to traditional tumor size.

Detection of a **PNT** may significantly alter the surgical resection &/or the radiation treatment field. Both mucosal and skin SCCa exhibit neurotropism, as do some salivary gland tumors and lymphomas. PNT is usually more evident on MR but may be detected on CT with careful evaluation of skull base foramina and known routes of spread.

Metastatic **nodal disease** is the most important prognostic factor in H&N SCCa. Prognosis worsens in H&N SCCa with increasing number of nodes and nodal chains, bilateral nodes, and lower level neck nodes. Lymph node metastasis reduces survival by 50% and doubles the incidence of distant metastasis. **ENE** reduces survival by a further 50%, and predisposes to a 10x increased recurrence risk, and 3x increased risk of distant metastasis. ENE is considered a high-risk, **poor prognostic** factor for all H&N tumors, **except viral-related cancers** [HPV (OPSCCa), EBV (NPCa)] and **mucosal melanoma**.

At the time of a staging neck CECT scan, lung apices and the bones should also be evaluated for **metastases**. Finally, many SCCa H&N cancer patients have increased risk of a **2nd primary neoplasm**. Second primary tumors are most frequently found with hypopharyngeal SCCa, and 1/3 are synchronous with the initial SCCa.

After surgery, radiation, &/or chemotherapy, **posttreatment baseline** imaging should be obtained to confirm absence of **residual disease**. This also serves as a roadmap of an anatomically changed neck to aid in detection of **recurrent disease**. The initial posttreatment scan for almost all SCCa is a PET/CECT, which should be delayed ~ 10-12 weeks to minimize false-positive FDG uptake from posttreatment inflammatory changes. A baseline CECT study may be obtained at 8-10 weeks after chemoradiation, while postsurgical studies are often obtained at 10-12 weeks.

The **posttreatment baseline** scan following radiation &/or chemotherapy should show no evidence of residual disease. The presence of enlarged nodes or residual primary mass

Sites and Subsites of Head and Neck Squamous Cell Carcinoma

1. Nasopharynx	3. Oral cavity	4. Hypopharynx
Fossa of Rosenmüller	Oral tongue	Posterior hypopharyngeal wall
	Floor of mouth	Pyriform sinus
2. Oropharynx	Alveolar ridge: Maxilla	Postcricoid region
Palatine tonsil	Buccal mucosa	**5. Larynx**
Posterior oropharyngeal wall	Lip	Supraglottis
Soft palate	Hard palate	Glottis
Lingual tonsil/base of tongue	Retromolar trigone	Subglottis
	Alveolar ridge: Mandible	

following treatment is of concern and is typically surgically resected. Posttreatment neck dissections are ideally performed < 10 weeks to minimize the complexity of surgery that results with neck fibrosis. So-called borderline soft tissue at baseline CT/MR may be carefully watched, may undergo US-guided aspiration, or may be resected.

Radiation therapy has changed enormously the last 2 decades with increasing use of **IMRT** for H&N cancers. IMRT maximizes dose to tumor, minimizes radiation to normal surrounding tissues, and requires accurate delineation of tumor margins. More input from radiologists to ensure accurate treatment volumes may be needed with MR, PET/CECT, or CECT alone. Radiation ± **chemotherapy** results in significant changes to appearance in neck soft tissues. Radiation results in acute inflammation and edema of all tissues in the radiation field. Over time, this changes to fibrosis, atrophy, and altered appearances on CECT and MR.

Surgical resection of a primary tumor &/or cervical neck nodes also results in changes to normal neck contours. Familiarity with the types of nodal **neck dissections** and common **flap reconstructions** helps evaluate both complications and recurrence. Knowledge of what surgical procedure was performed prior to evaluating posttreatment imaging is critical. Some resections, such as selective neck dissections, can be subtle on imaging, while large resections with flap reconstructions can be quite complex. MR is less affected by hardware artifact and more sensitive for recurrent tumors; however, the muscular component of a flap reconstruction undergoes denervation changes, resulting in variable MR signal intensity and enhancement. On the baseline scan following neck reconstruction, residual or progressive tumors should be described.

Recurrent SCCa most often occurs in the first 2 years after initial treatment. Frequency of **surveillance imaging** during this time is variable and may be performed in 3- to 6-month intervals, depending on initial tumor stage, prognostic features, and clinical course, including physical findings. At the follow-up imaging examination, the possibility of a **2nd primary tumor** must be considered. Remember to look for **residual, recurrent, and new** tumors on each follow-up study.

How to Stage New Tumor With CT or MR

- Determine site of primary; open TNM staging table for specific primary site
- Evaluate size and local extent of tumor; what is deep extent; is there bone marrow infiltration; is there PNT; how far does it go in each direction; primary is best described in dedicated paragraph in report
- Evaluate regional drainage nodes and contralateral node(s); are there retropharyngeal nodes
- Evaluate included lungs and bones for metastases
- PET/CT or PET/MR greatly increases staging accuracy

How to Read Posttreatment Scan

- Compare pretreatment scan, history of original tumor stage, treatment and time since treatment; confirm on scans what, if anything, has been resected; be aware that selective neck dissections may be subtle; is there reconstruction flap
- Evaluate effects of radiation and become familiar with posttreatment appearances; look for residual/recurrent tumor at primary site
- Evaluate for adenopathy through entire neck, especially if some levels were dissected previously; drainage patterns may change
- Consider possibility of 2nd primary tumor, especially if history of excessive smoking/alcohol: H&N mucosal SCCa, lungs, cervical esophagus; evaluate lungs and bones for metastases

Clinical Implications

If a primary site is not evident on clinical examination in a patient with a new neck mass that is nodal SCCa (**unknown primary tumor**), 4 key sites should be evaluated for the asymmetric soft tissue of an unknown primary tumor in a neck CECT or MR: (1) Nasopharynx: **Fossa of Rosenmüller**, (2) oropharynx: **Palatine tonsil**, (3) oropharynx: **BOT or lingual tonsil**, and (4) hypopharynx: **Apex of pyriform sinus**. The fossa of Rosenmüller and pyriform sinus apex may be clinical "blind spots," either at the in-office examination or, if very small, even at direct endoscopy. The palatine and lingual tonsils may harbor a tumor in the depths of crypts, so the mucosal tumor may not be evident visually or on palpation.

The rising incidence of HPV(+) OPSCCa makes it imperative that the radiologist is vigilant when evaluating a younger, nonsmoking subset of patients presenting with a new neck mass, which may be a cystic/necrotic or solid metastatic node. **A new neck mass in an adult, unless a thyroid goiter, should be assumed neoplastic until proven otherwise.**

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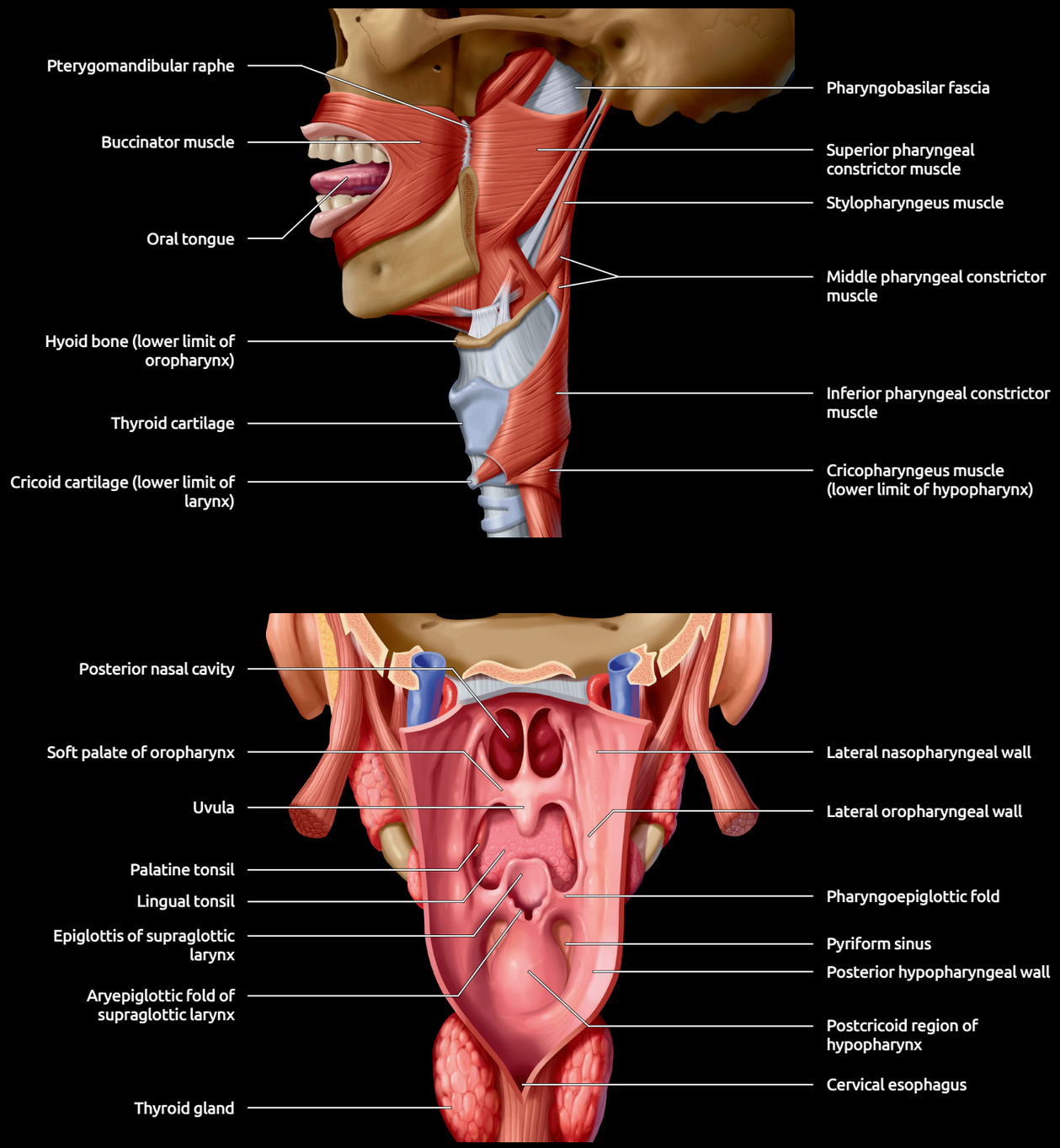
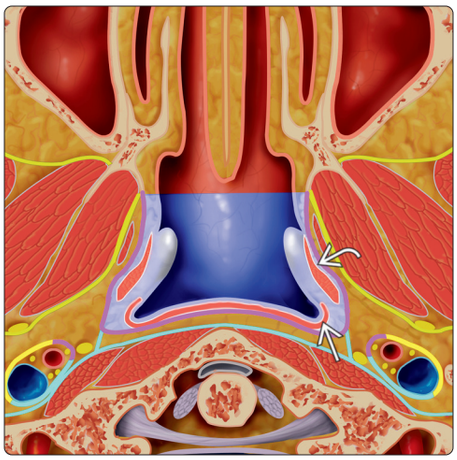
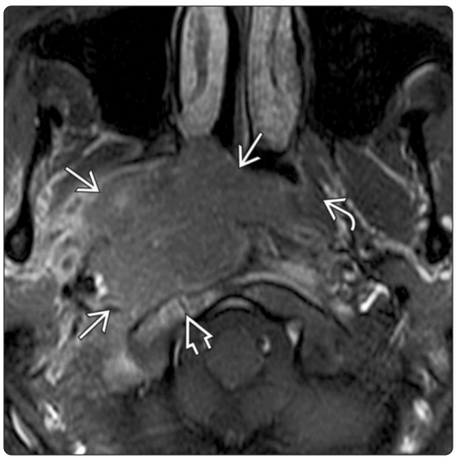


(Top) *Lateral graphic shows the major muscles of the pharyngeal mucosal space. Notice that the pharynx is essentially a tube attached superiorly to the skull base and formed from the superior, middle, and inferior pharyngeal constrictor muscles. The nasopharynx, oropharynx, and hypopharynx are contiguous segments of this tube with the oral cavity contiguous anteriorly with the oropharynx. The larynx is intimately related to the hypopharynx and originates at the lower aspect of the oropharynx.* **(Bottom)** *Graphic of the pharyngeal mucosal space/surface as if opened from behind shows that this space can be divided into nasopharyngeal, oropharyngeal (OP), and hypopharyngeal areas. The lymphatic ring of the pharyngeal mucosal space (Waldeyer) contains the nasopharyngeal adenoids and the OP palatine and lingual tonsils or base of tongue.*

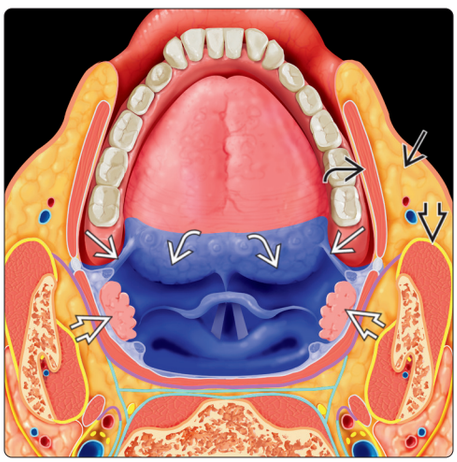
Squamous Cell Carcinoma Overview

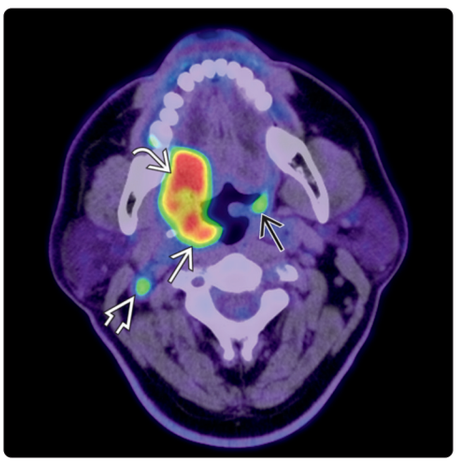
(Left) *Axial graphic of the nasopharyngeal mucosal space (blue) shows superior pharyngeal constrictor and levator veli palatini muscles within the space. The middle layer of deep cervical fascia (pink line) provides a deep margin to the space.* **(Right)** *Axial T1 C+ FS MR in a young Asian woman with trismus shows a large, mildly enhancing nasopharyngeal carcinoma, infiltrating right masticator space & clivus. Note normal left levator veli. MR is better for skull base (T3) & intracranial or cranial nerve (T4) infiltration.*



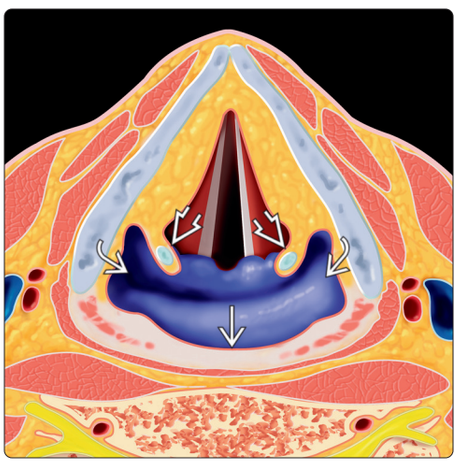


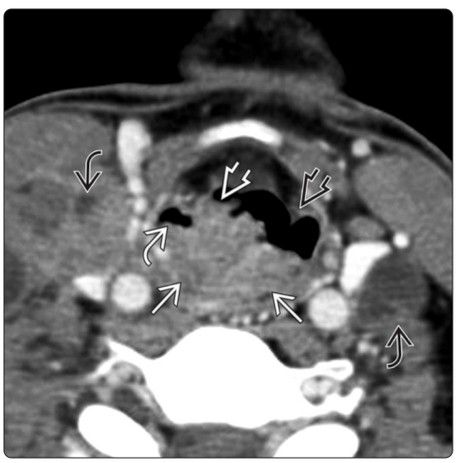
(Left) *Axial graphic shows OP mucosal space (blue) and more anterior oral cavity (red). Note anterior tonsillar pillar, palatine tonsil, and lingual tonsil (base of tongue). The fat-filled (yellow) buccal space is bounded medially by buccinator muscle, posteriorly by masseter and parotid, and anterolaterally by facial muscles.* **(Right)** *Axial fused F-18 FDG PET/CT shows FDG-avid HPV(+) OPSCCa in right palatine and lingual tonsils. Note metastatic lymph node The left tonsil high FDG uptake is physiologic.*

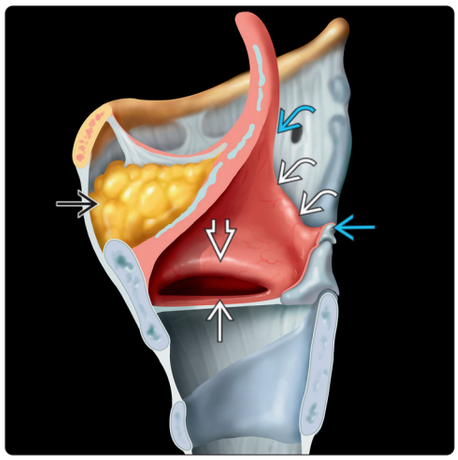


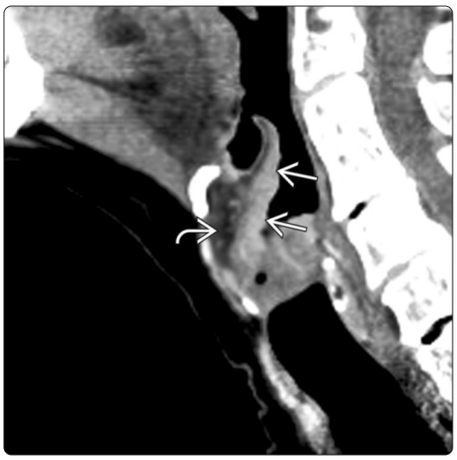


(Left) *Axial graphic shows the hypopharyngeal aspect of the pharyngeal mucosal space. At the level of the supraglottis, the hypopharynx is made up of the pyriform sinus (PS) & posterior hypopharyngeal wall (PHW). Aryepiglottic (AE) folds are part of the supraglottis, & separate larynx from hypopharynx.* **(Right)** *Axial CECT shows extensive bilateral adenopathy with an irregular, superficially spreading mass arising from PHW, involving right PS wall & the marginal supraglottic AE fold. Note normal left AE fold.*

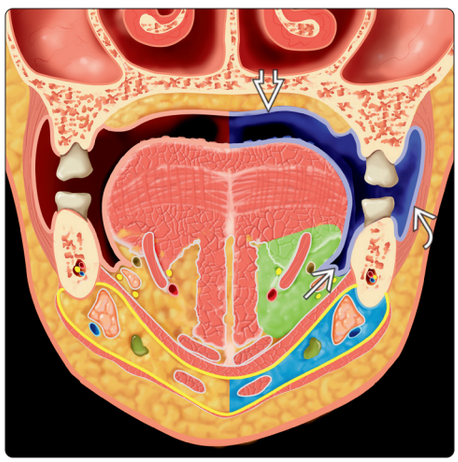


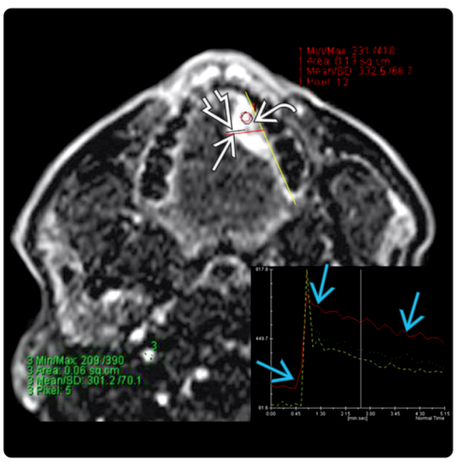




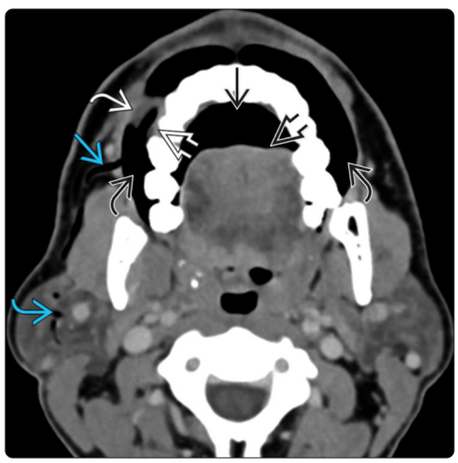


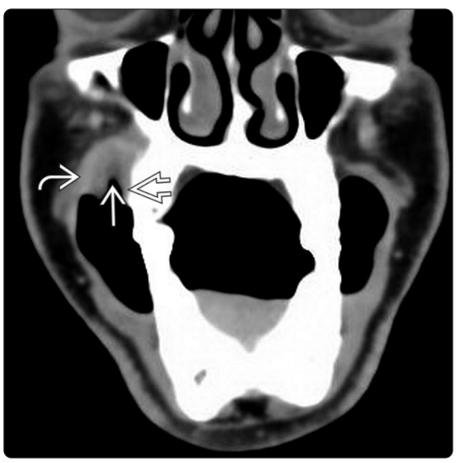
(Left) *Sagittal graphic of larynx shows true vocal cord ➡ of glottic larynx. The false cord ➡ lies above & parallels this, while the AE fold ➡ projects from the arytenoid cartilage tip ⇨ to epiglottic inferolateral margin ⇨. Note fat in preepiglottic space ⇨. Subglottis extends from below true cords to lower cricoid margin.* **(Right)** *Sagittal CECT shows abnormally thickened laryngeal surface of epiglottis ➡ in SCCa. The supraglottic larynx includes the epiglottis, AE folds, & false cords with fatty anterior preepiglottic ➡ & lateral paraglottic spaces.*





(Left) *Coronal graphic shows oral mucosal surfaces (blue) of hard palate ➡, oral tongue, upper & lower alveolar ridges, buccal space ➡, & floor of mouth ➡.* **(Right)** *Axial dynamic VIBE T1 C+ MR shows enhancing left anterolateral tongue SCCa with ulcerated ➡ surface. Tumor thickness (TT, black line) ➡ should be measured from tumor surface (at inner margin of ulcer here), & depth of invasion (DOI, red line) ➡ from tongue mucosal surface, to deepest point of tumor. ROI from tumor shows rapid rise with slow washout time-intensity curve (TIC) ⇨.*





(Left) *Axial puffed-cheek technique CECT shows the small soft tissue of a SCCa along the right maxillary gingival ➡ & buccal ➡ margins. Note air in the central oral cavity proper ⇨ outlining the oral tongue ⇨, air in lateral oral vestibules ⇨ separating buccal & alveolar gingival margins, and air entering the right main parotid duct ⇨ & ductules ⇨.* **(Right)** *Coronal reformatted CECT shows that the tumor spreads from the gingival mucosa ➡ through the superior gingivobuccal sulcus ➡ into the buccal region ➡.*