



Oncology
Learning Network

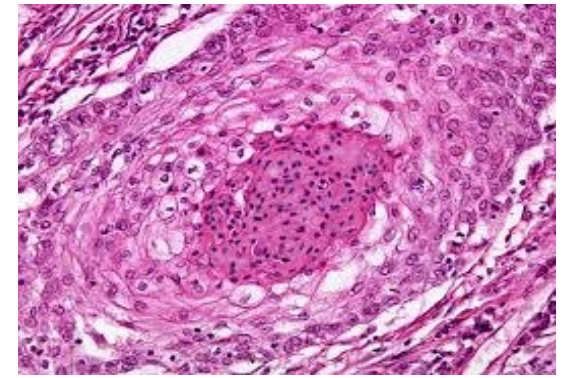
Optimizing the Patient Journey in Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Evolving Guidelines, Emerging
Options, and Multidisciplinary
Management Strategies

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Faculty



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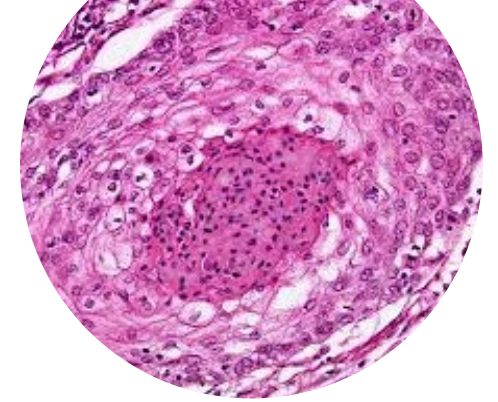
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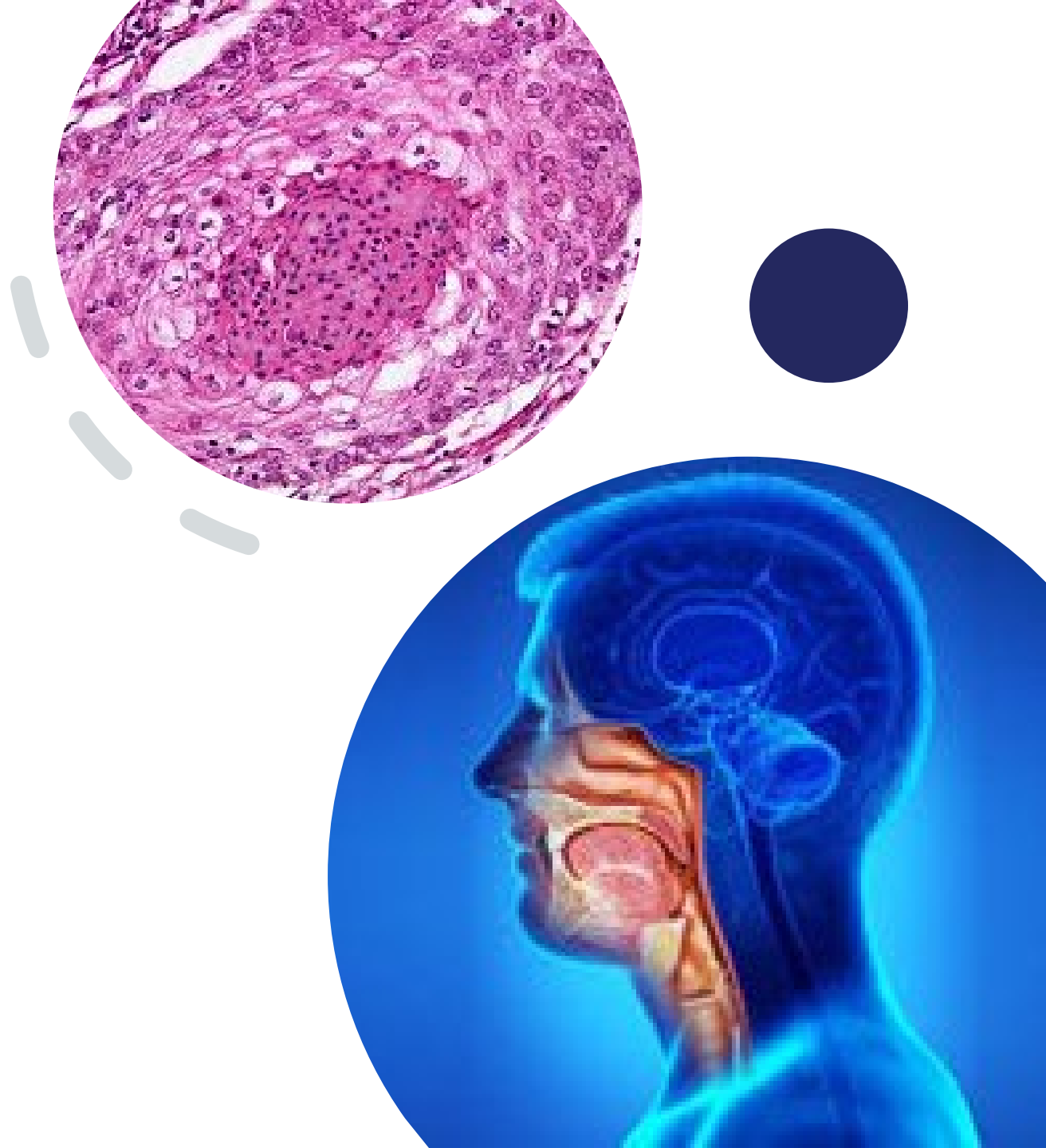
Faculty Disclosures

- **Faith Mutale, DNP, CRNP:** Speakers Bureau—Helsinn, Merck; Advisory Board—Pfizer
- **Erin McMenamin, PhD, CRNP,** has disclosed no relevant financial relationship with any ineligible company (commercial interest)



Program Information

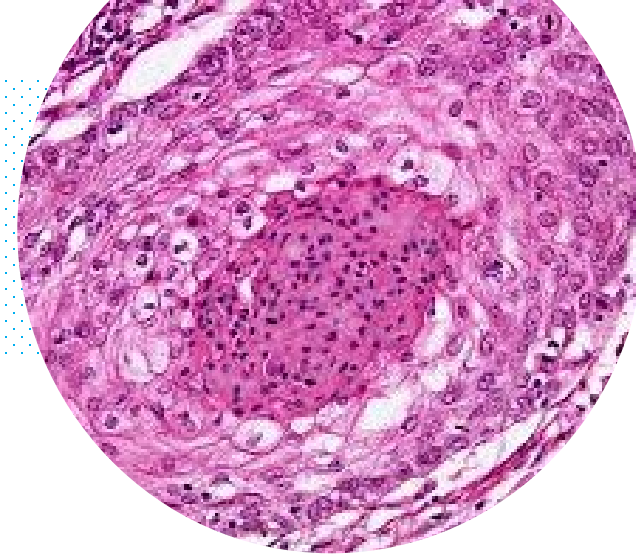
- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from EMD Serono, Inc.



LA SCCHN*

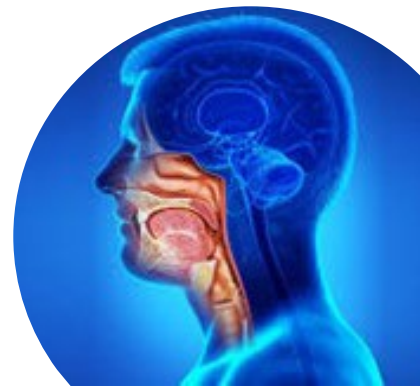
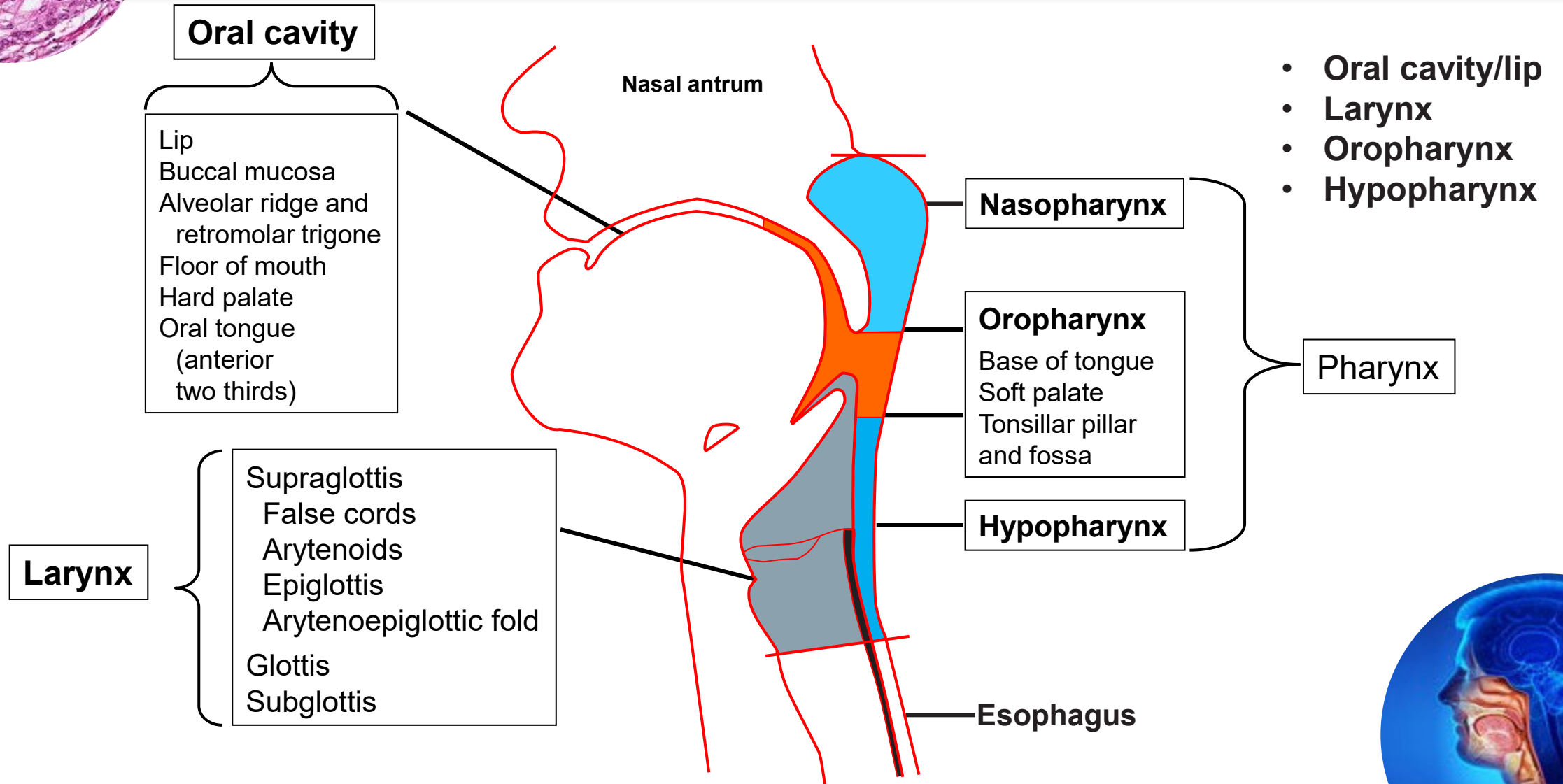
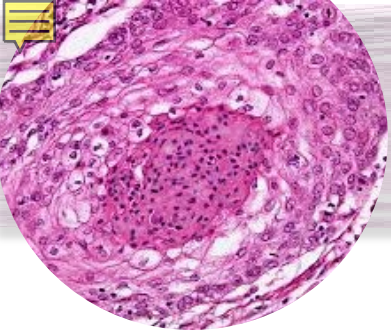
Learning Objectives

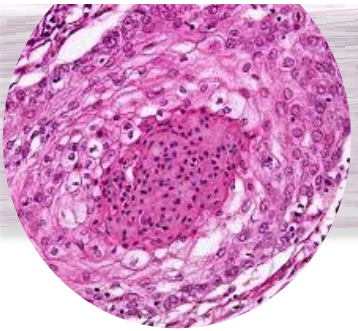
Describe	Describe the prevalence, burden, and management challenges associated with LA SCCHN and strategies to optimize recognition and assessment
Assess	Assess current management strategies for platinum-eligible and platinum-ineligible patients
Evaluate	Evaluate newer and emerging options for the treatment of LA SCCHN and potential implications for multidisciplinary treatment paradigms
Outline	Outline essential considerations and strategies for optimizing patient care among advanced practice providers for the management of LA SCCHN



*LA SCCHN = locally advanced squamous cell carcinoma of the head and neck.

Head and Neck Cancer





Epidemiology and Patient Burden

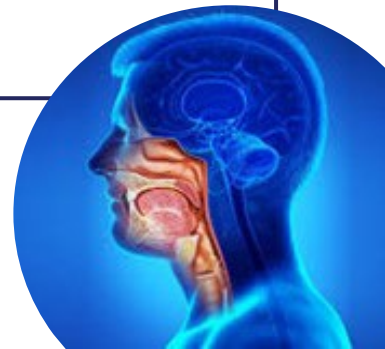
Global

- ~900,000 new cases/year
- ~400,000 deaths/year
- M:F ratio 2:1-4:1
- Approximately 60% of SCCHN cases are locally advanced at the time of diagnosis



USA

- 58,450 new cases/year (oral cavity and pharynx)
- 12,230 deaths/year
- Average annual percentage change 1.0 vs 0.4% male vs female incidence
- Lower rates of HPV-related cancer compared to some developing countries
- HPV-related HNC has surpassed cervical cancer incidence in the US and UK



HPV = human papillomavirus; HNC = head and neck cancer.

Barsouk A, et al. *Med Sci (Basel)*. 2023;11(2):42. American Cancer Society. Accessed October 31, 2024.

<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acf.pdf>; <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-2024.pdf>.

Histology

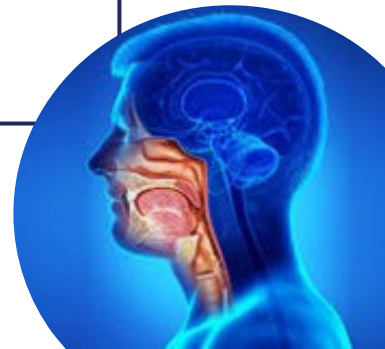


Squamous Cell

- Tongue
- Tonsil
- Larynx
- Hypopharynx
- Nasopharynx
- Nasal cavity
- Paranasal sinus
- Skin

Non-squamous Cell

- Thyroid
- Salivary gland
- SNEC (rare)
- SNUC (rare and aggressive), few EBV+
- Adenoid cystic
- Tonsil lymphoma
- Sarcomas
 - Soft tissue and hard tissue



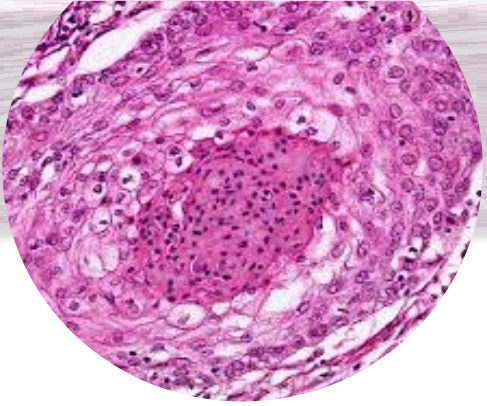
Head and Neck Cancer Subtypes

Focus: Head and Neck Squamous Cell Carcinoma (HNSCC)

- HPV-positive (HPV+)
 - Oropharynx
- HPV-negative (HPV-)
- Unknown primary

Primary Risk Factors

- Tobacco
- Alcohol use
- Infections
 - HPV
 - EBV
- Betel (areca) nut chewing
- Immunodeficiency



HPV-Positive Cancer

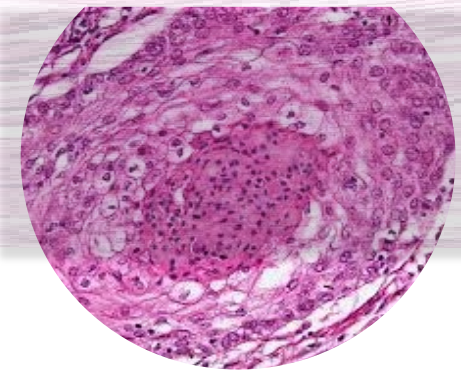
- Newer subtype
- Increasing incidence
- >80% oropharynx
- Gender, racial, and economic differences
- Distinct patterns of metastasis

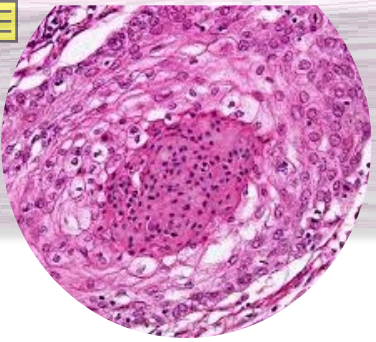
HPV Testing

- Robust testing required to differentiate HPV+ vs HPV- disease
- Use p16 IHC as surrogate for HPV status
- In-situ hybridization for high-risk disease
 - Sensitivity: 97%
 - Specificity: 94%
- Important to inform de-escalating therapies in HPV+ cancer

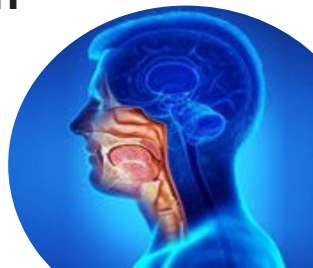
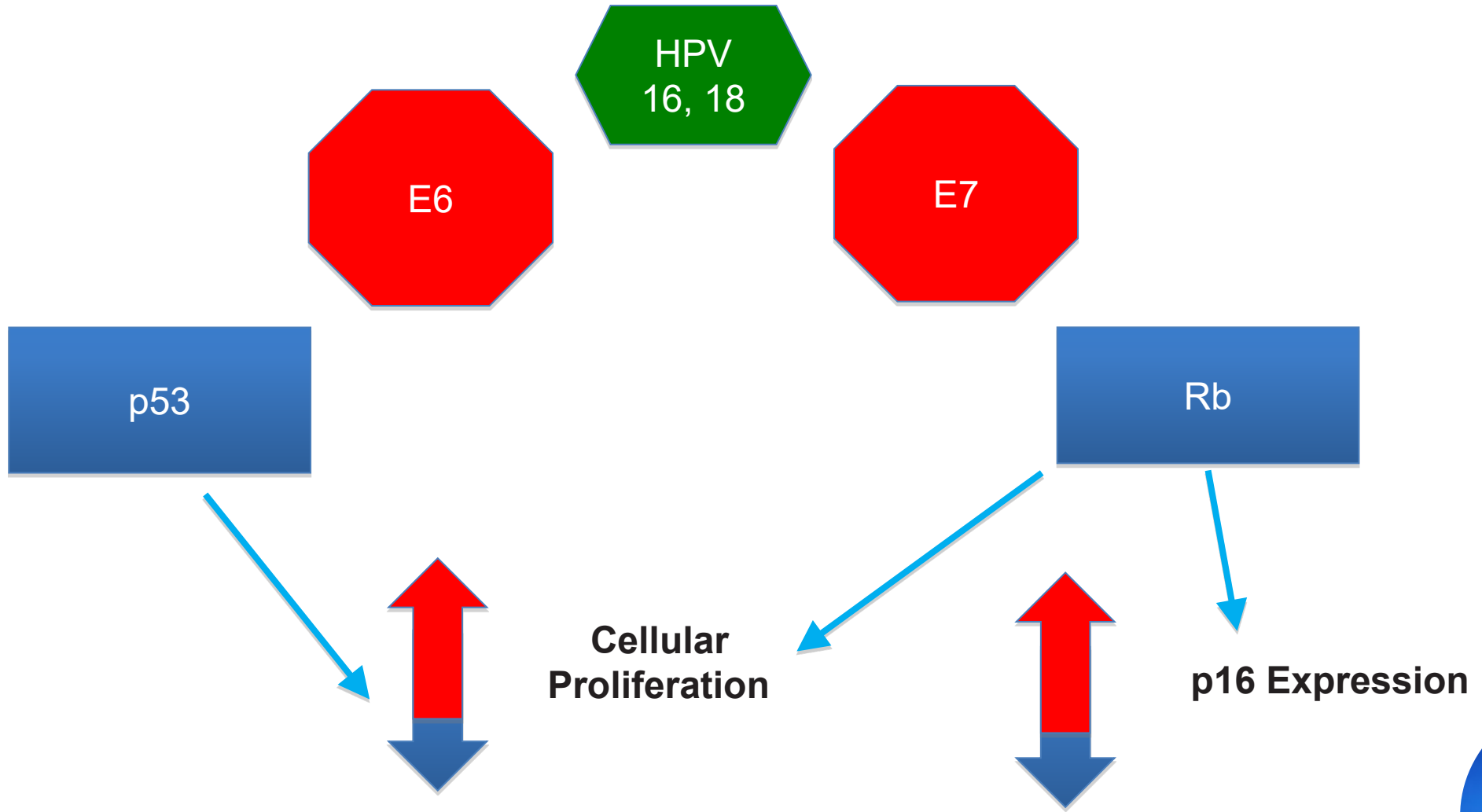
IHC = immunohistochemistry.

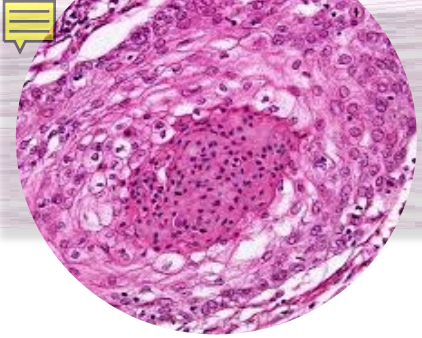
Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327.



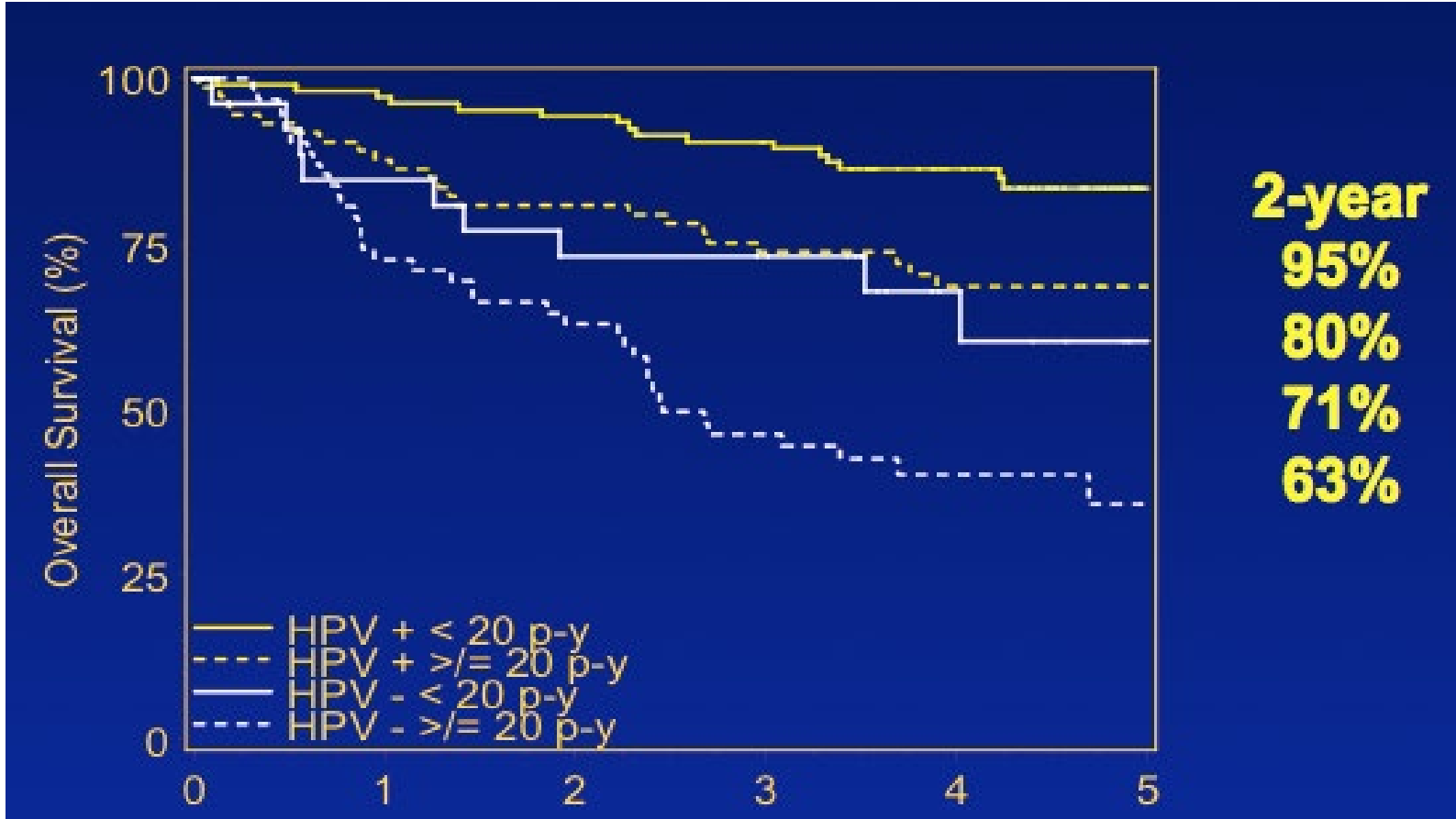


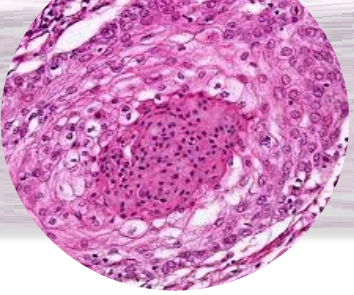
High-Risk HPV





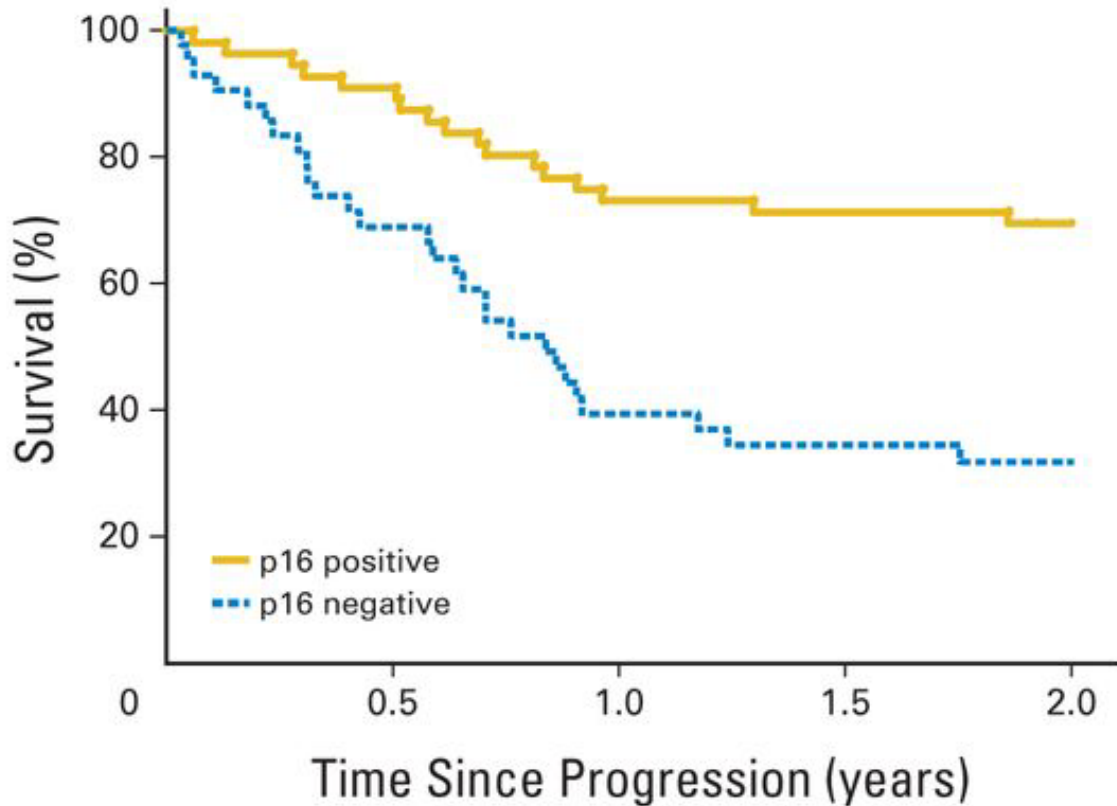
Prognostic Disparity Based on HPV Status



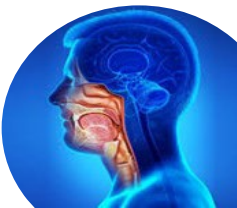
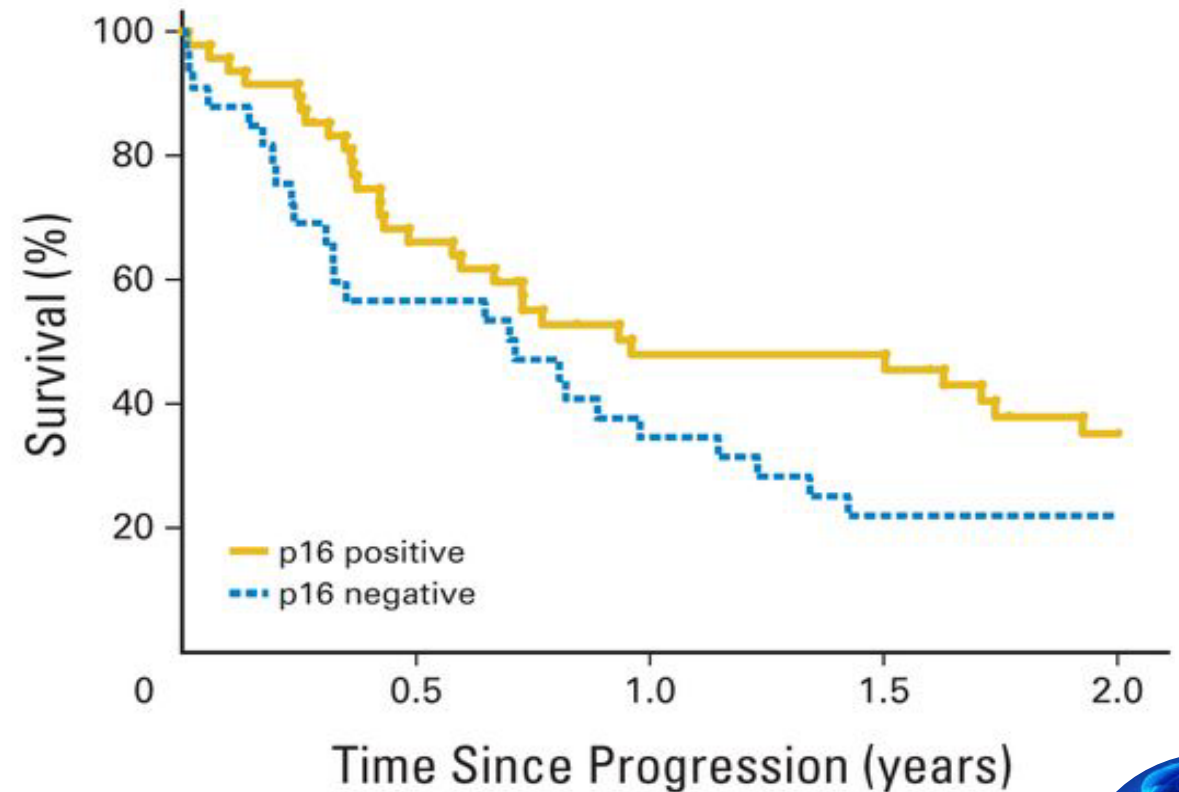


Prognostic Impact of HPV after Metastasis

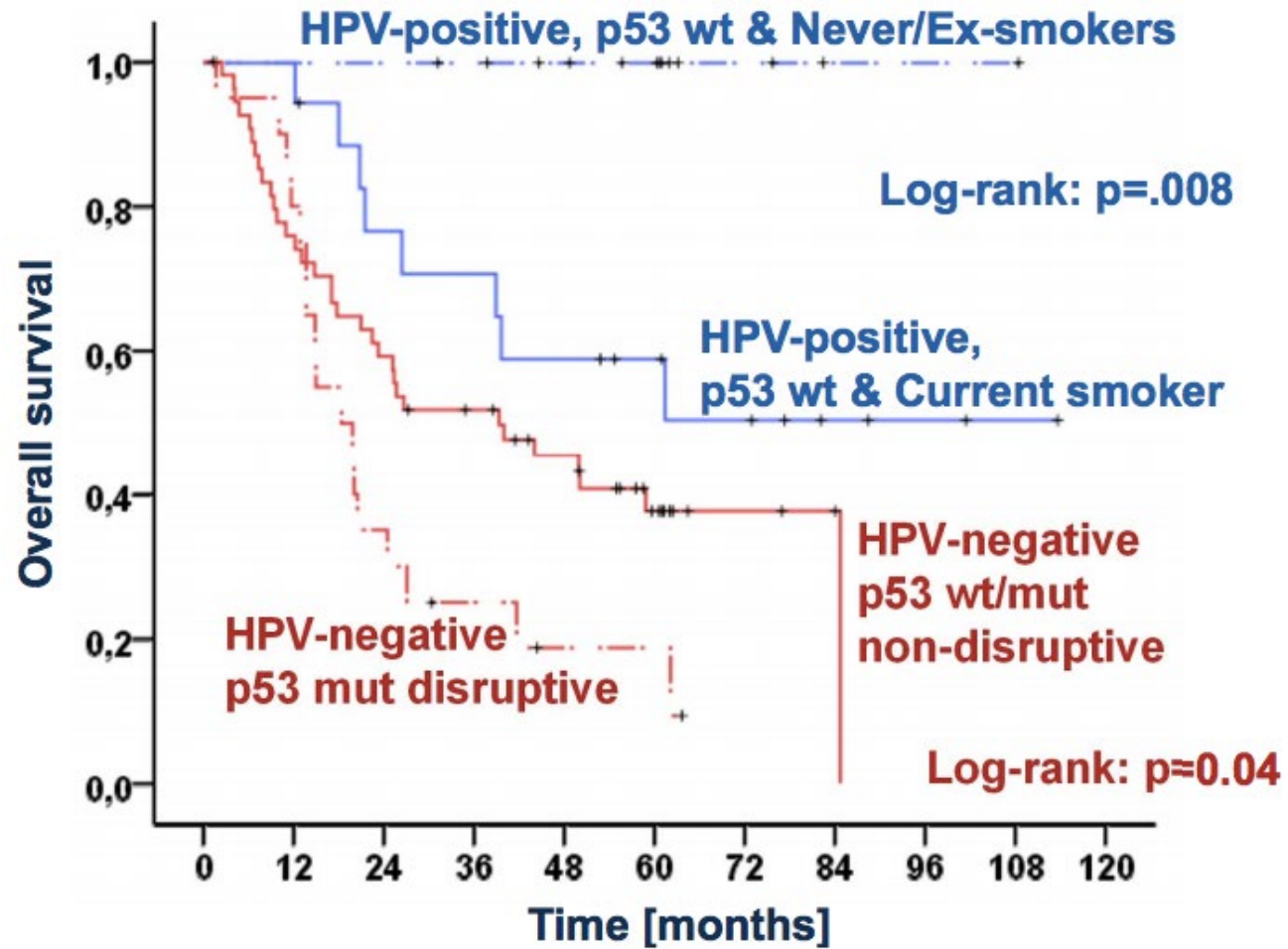
Locoregional Recurrence

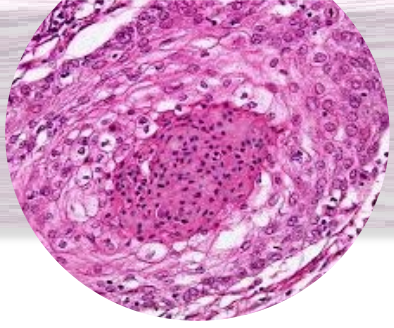


Distant Metastases



Understanding Genetics Improves Prognosis





Head and Neck Cancer

HPV-Positive (+)

- Younger patients (biphasic, peaks at 30 and 55)
- >Male 4:1
- Minimal or non-smoker
- Higher number of sexual partners and oral sex frequency
- Oropharynx: BOT, tonsil, soft palate
- Lymph node involvement (asymptomatic neck mass)
- Smaller primaries
- Better prognosis
- p16 surrogate marker



VS

HPV-Negative (-)

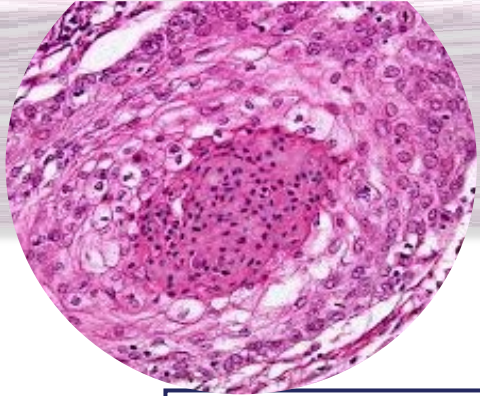
- Older patients (median age 61)
- Male 3:1
- Extensive smoking history and alcohol use
- Tobacco chewing
- All sites: larynx, hypopharynx, oral cavity, oropharynx
- Dysphagia, hoarseness, weight loss
- Pain: odynophagia, otalgia
- Single or multiple large primary tumors ± LN
- Poor prognosis



BOT = base of tongue; LN = lymph node.

Barsouk A, et al. *Med Sci (Basel)*. 2023;11(2):42. Fong PY, et al. *Eur Arch Otorhinolaryngol*. 2024;281(5):2645-2653.

p16 and HPV Discordance



p16+/HPV+

- Better prognosis
- Never or former smokers
- Not site-dependent

p16+/HPV-

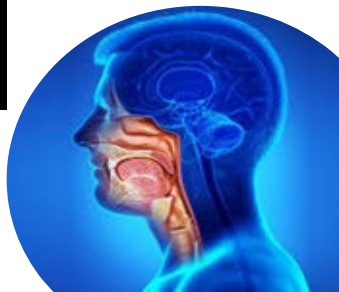
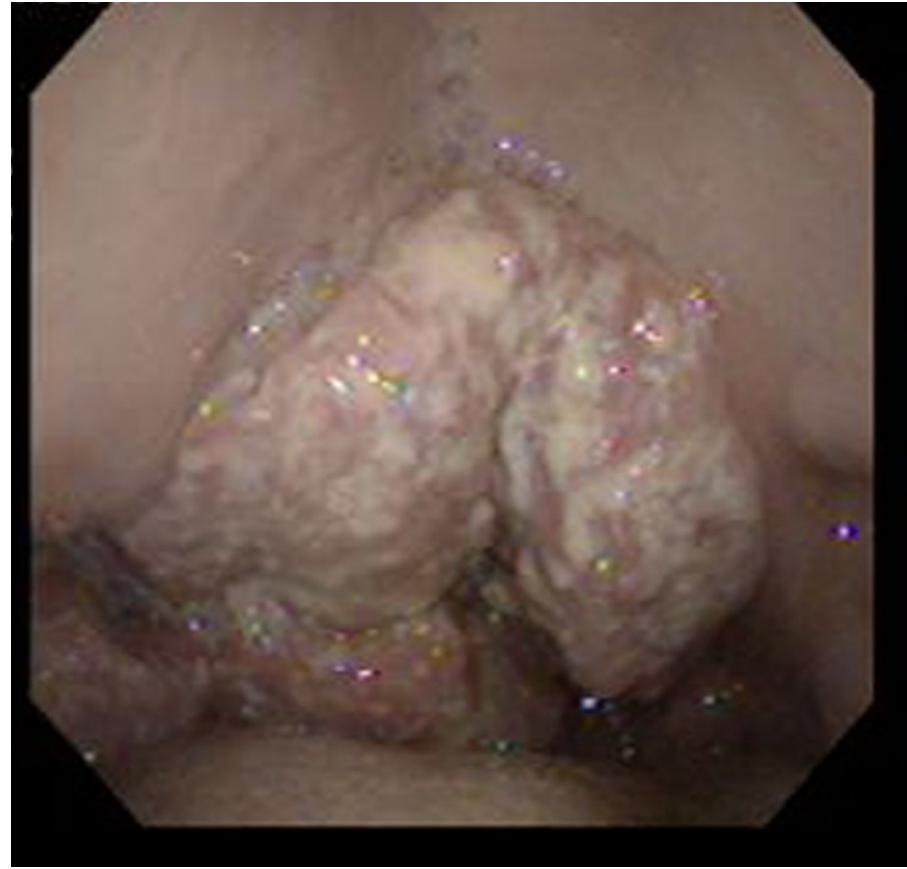
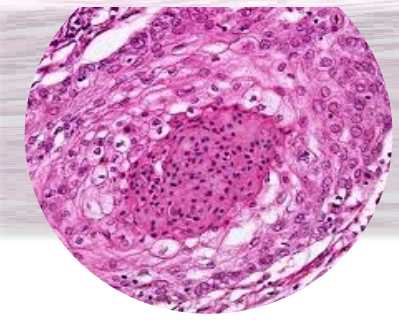
- Worse prognosis but better than in patients with p16-/HPV-
- Lower 5-year OS
- Common in areas with low HPV prevalence

OS = overall survival.

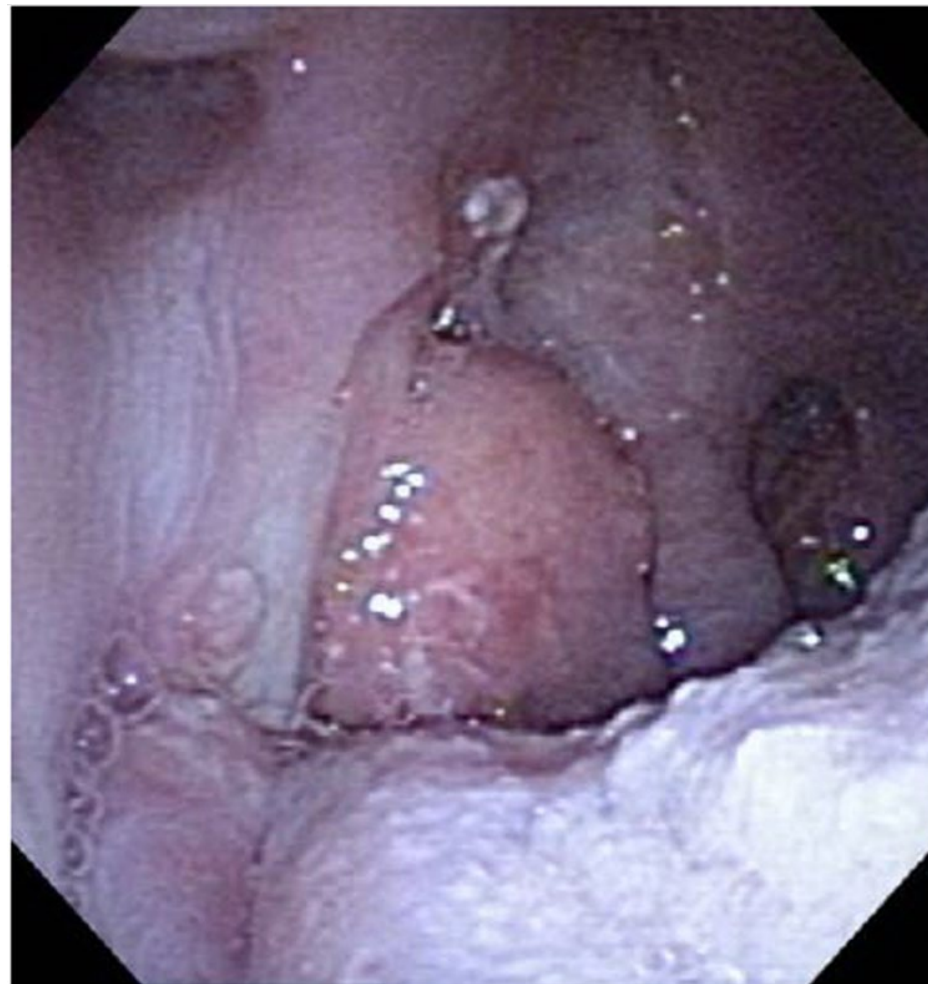
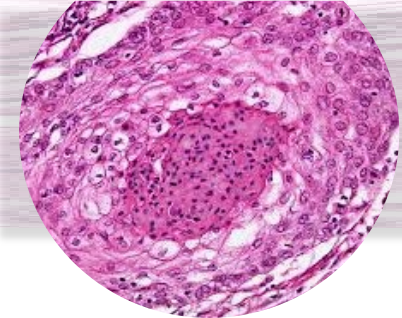
Lechner M, et al. *Nat Rev Clin Oncol.* 2022;19(5):306-327. Mehanna H, et al. *Lancet Oncol.* 2023;24(3):239-251.



p16+ Tonsil Cancer: Pre-Induction



p16+ Tonsil Cancer: Post-Induction



Summary




>90% of SCCHN is HPV+

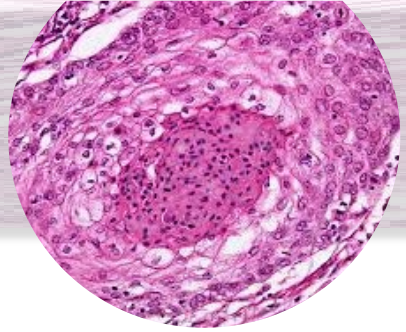
p16+ tumors have an improved prognosis

20% of p16+ is false positive

Pipeline trials evaluating de-escalation therapies in HPV+ disease

p16 is a prognostic, not predictive biomarker





Signs and Symptoms

Variable

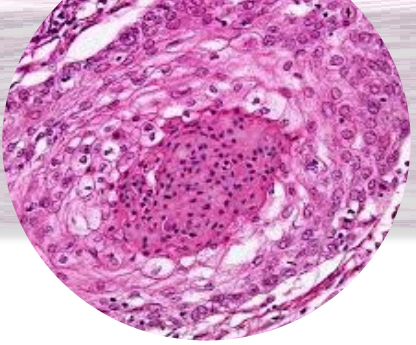
Primary site

Nodal involvement

Size of tumor



Diagnostics: Direct Visualization



History and physical exam

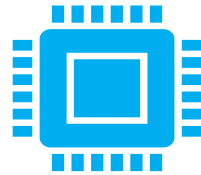


Inspection

Direct laryngoscopy

Panendoscopy (laryngoscopy, bronchoscopy, and esophagoscopy)

Fiber-optic endoscopy for visualization of nasopharynx, oropharynx, hypopharynx, and larynx

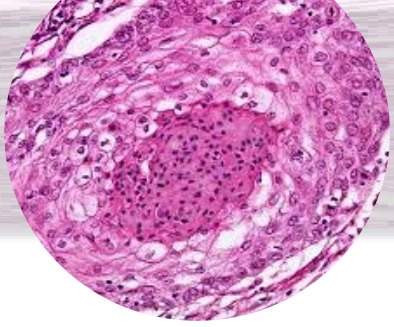


Exam under anesthesia (EUA)

Tissue diagnosis



Diagnostics: Imaging



PET/CT scan: characterization of tumor and met disease evaluation



CT scan neck: evaluation of ECS and nodal metastasis



MRI: tongue lesions, perineural spread, skull base, and intracranial invasion



CT scan chest



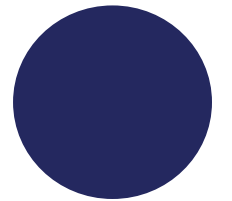
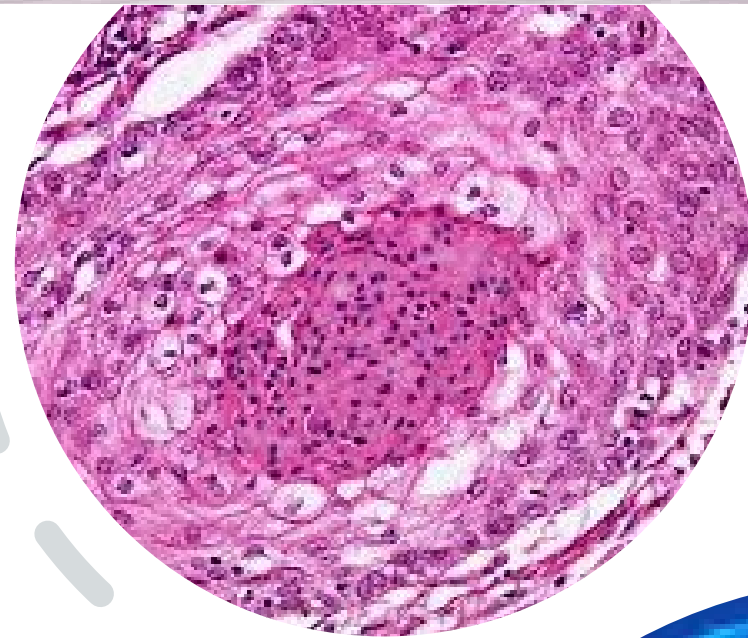
Chest X-ray

PET = positron emission tomography; CT = computed tomography; ECS = extracapsular spread; MRI = magnetic resonance imaging. Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327. Stenson KM, et al. UpToDate. Last updated June 28, 2024. Accessed October 31, 2024. <https://www.uptodate.com/contents/overview-of-the-diagnosis-and-staging-of-head-and-neck-cancer>.

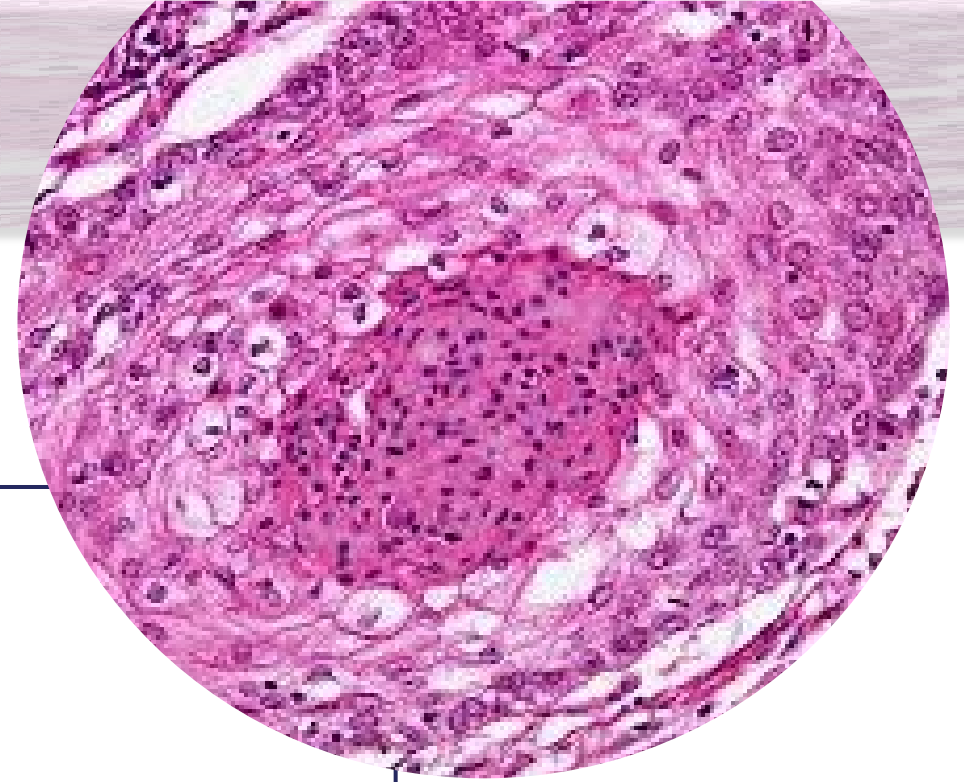


Diagnostics: Biopsy

- Fine-needle aspiration
- Sentinel lymph node biopsy (SLNB): midline malignancies with ipsilateral disease



Second Primary Tumors

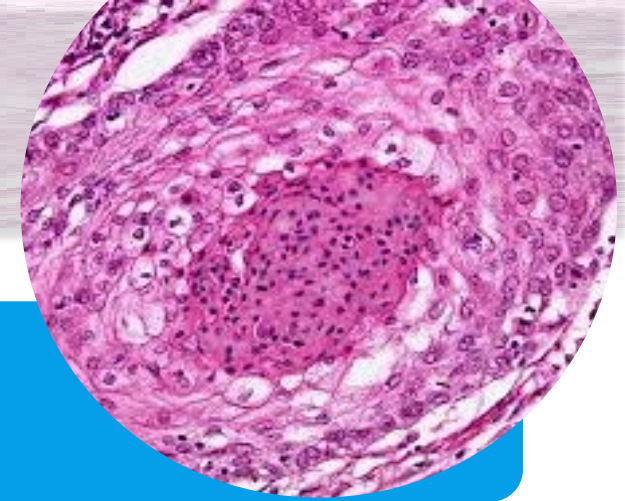


RISK

- Smokers and tobacco users
- Initial presentation or appears later



Staging



8th edition **TNM** system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control

The **T** classifications indicate the extent of the primary tumor and are site-specific

Considerable overlap in the cervical **N** classifications

TNM staging varies depending on the primary tumor site



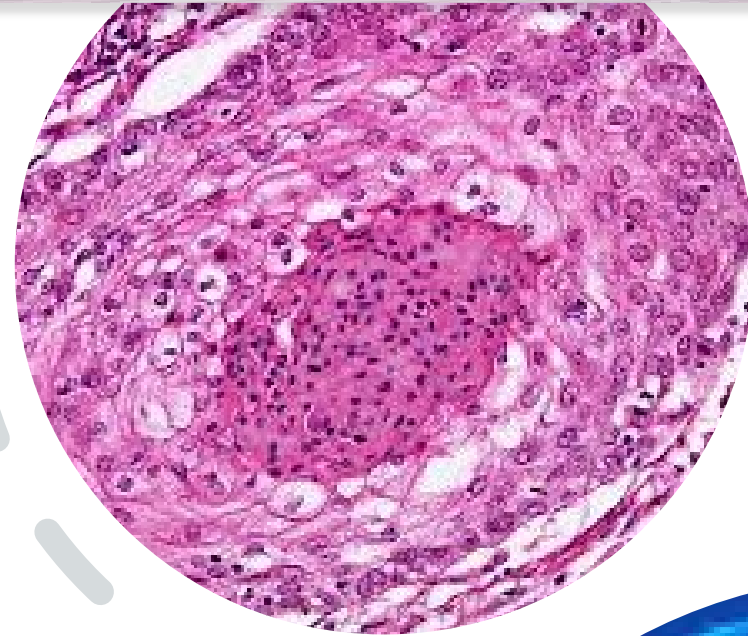
TNM = tumor, node, metastasis.

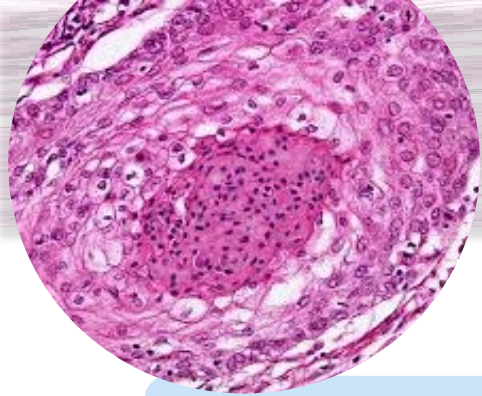
Bhatia A, et al. *Drugs*. 2023;83(3):217-248. Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327. Stenson KM, et al. UpToDate. Last updated June 28, 2024. Accessed October 31, 2024. <https://www.uptodate.com/contents/overview-of-the-diagnosis-and-staging-of-head-and-neck-cancer>.

Staging: HPV+

2018 AJCC
8th edition
TNM

Prior stage
IVA: I, II,
and III





Molecular Staging: Pipeline Research



Evaluation of differences in gene expression patterns



Provide information

Classification

Prognosis

Treatment options



Molecular profiling

Predict radiosensitivity or toxicity

Chemo-induced ototoxicity (COMT and MATE1)

ctDNA: driver mutations

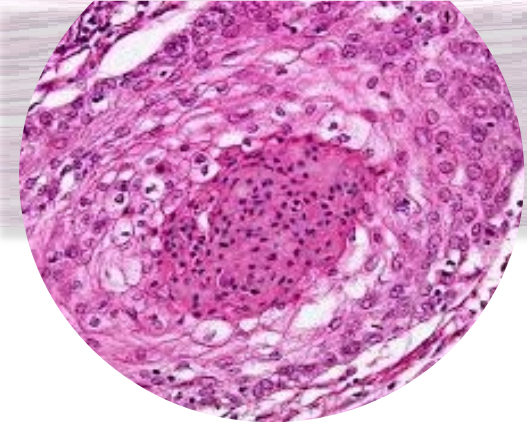


ctDNA = circulating tumor DNA.

Stenson KM, et al. UpToDate. Last updated June 28, 2024. Accessed October 31, 2024.

<https://www.uptodate.com/contents/overview-of-the-diagnosis-and-staging-of-head-and-neck-cancer>.

Management Strategies: Guidelines



National
Comprehensive
Cancer Network

College of
American
Pathologists

American
Society of
Clinical
Oncologists

National Comprehensive Cancer Network (NCCN). Accessed October 31, 2024. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437>. College of American Pathologists. Accessed October 31, 2024. <https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/human-papillomavirus-testing-in-head-and-neck-carcinomas>. American Society of Clinical Oncologists. Accessed October 31, 2024. <https://society.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2018-HPV-Endorsement-Slides.pdf>.



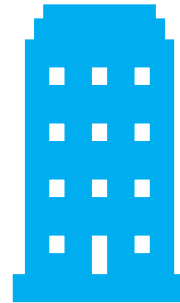
Management Strategies



Complex

Decision-making influenced by clinical factors

Multidisciplinary effort

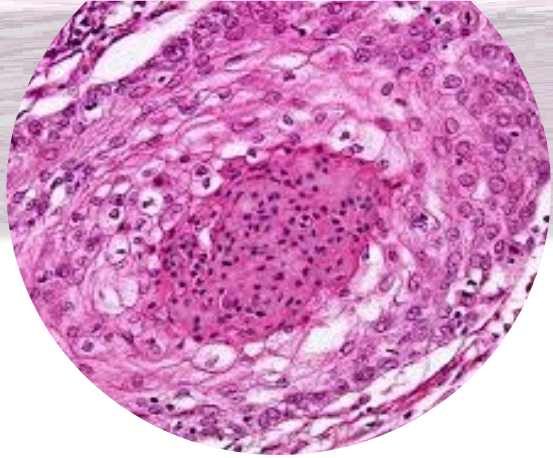


High-volume centers
preferred for treatment



RTOG trial (RTOG 0129)
improved 5-year survival seen
among patients enrolled from
centers with historically high
accrual to head and neck clinical
trials

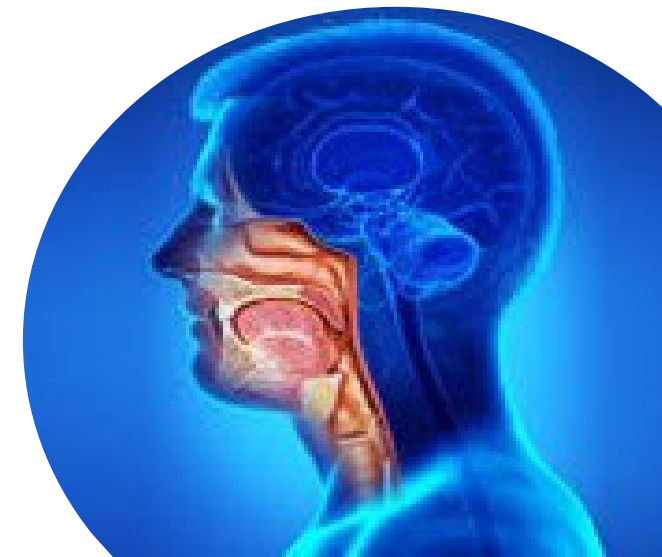




Management Strategies

Multidisciplinary Team Approach

- Surgeon, medical, and radiation oncologists
- Dentists, prosthodontists
- Advanced practice professionals (NPs, PAs)
- Speech/swallowing pathologists
- Dietitians, social workers
- Physical/rehabilitation therapists
- Tumor board



NP = nurse practitioner; PA = physician assistant.

Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327. NCCN. Accessed October 31, 2024.

<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437>.



Management Considerations



Goals of care or purpose of the considered therapy?



Benefits vs toxicities: potential to do harm, worsen quality of life



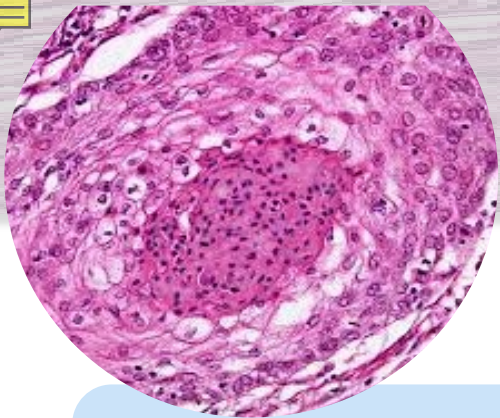
Performance status



Supportive care approach may be appropriate



Management



Localized/early stage: 30-40%

Surgery

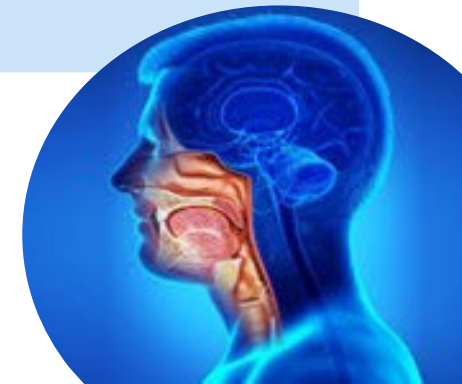
Radiation

5-year survival: 70-90%

Chemo if with lymph node involvement, LVI, PNI, ECS, positive surgical margins



Increased risk for second primaries and lung cancer (smokers)

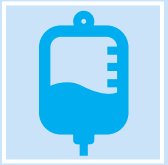
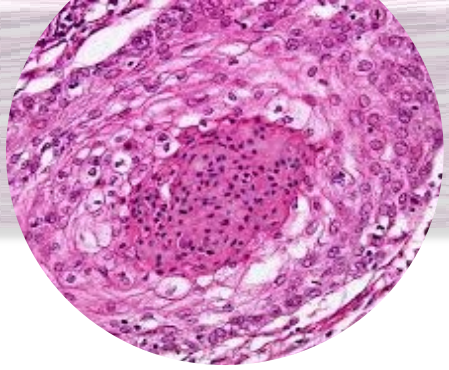


LVI = lymphovascular invasion; PNI = perineural invasion.

Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327. Maring S, et al. *Oncol Res Treat*. 2018;41(12):736-743. NCCN.

Accessed October 31, 2024. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437>.

Management



Locally advanced disease
(stage III/IV)

Increased risk:

Recurrence and Distant Metastasis

Combined modalities:

Surgery, RT, or CRT



Considerations

Primary site

Surgery preferred for oral cavity, aggressive cancers, and postoperative RT necessary due to high recurrence rates

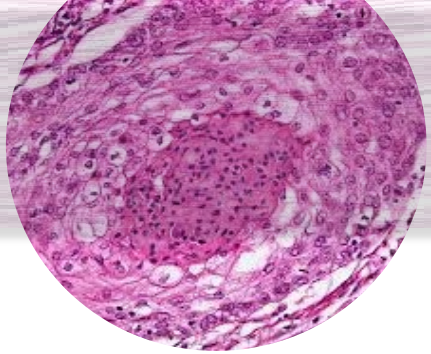
Age

Comorbidities



RT = radiation therapy; CRT = cardiac resynchronization therapy.

Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327. Michelon I, et al. *J Cancer Res Clin Oncol*. 2024;150(8):379. NCCN. Accessed October 31, 2024. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437>. Xu B, et al. *Mod Pathol*. 2022;35(11):1578-1586.



Nasopharynx Cancer

Relatively rare in the US

- More common in Asia, often associated with EBV
 - In the US: smoker/drinker disease
- Similar to HPV, EBV+ NPC is likely a different disease than EBV- NPC

Rapid growth, responsive to CRT

- Need to balance toxicity of therapy with efficacy

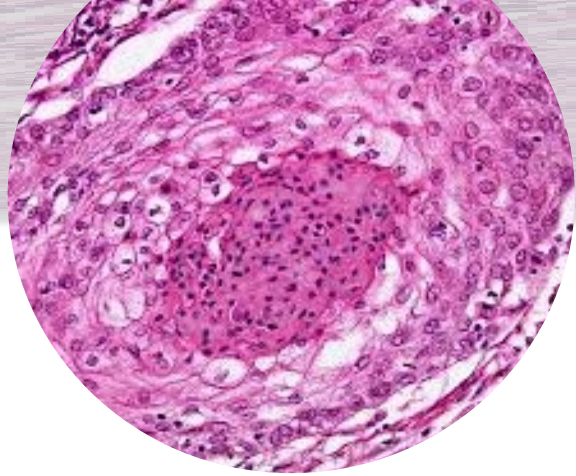
CRT improves survival in locally advanced disease



NPC = nasopharynx cancer.

Bhatia A, et al. *Drugs*. 2023;83(3):217-248. Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327.

Nasopharynx Cancer



Endemic

- SE Asia, North Africa
- EBV+
- Better prognosis
- Better response to IO
- Somatostatin receptor 2 (SSTR₂)
→ PDL1 high (trials)

Sporadic

- Global
- EBV-
- Poor prognosis
- Poor response to IO



Nasopharynx Cancer: Management



**Pathology, natural history,
and treatment**



**Traditionally unresectable
due to its location**

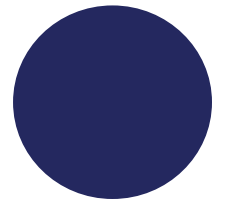
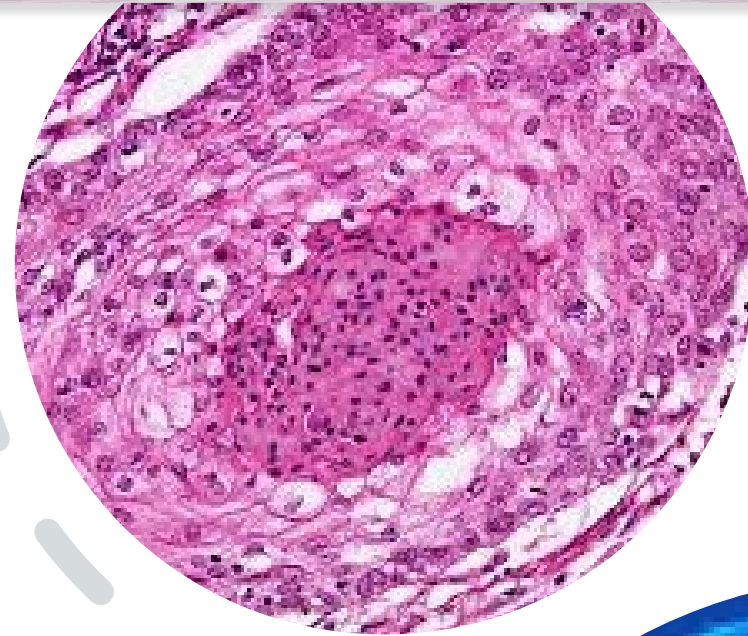


**RT is primary treatment for
early stage**

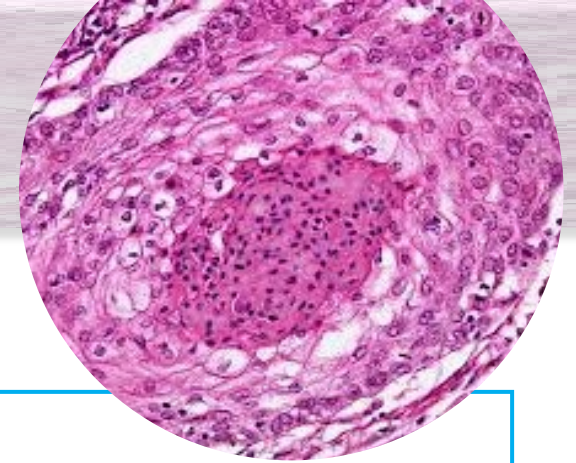


Salivary Gland Cancers: Management

- **Parotid**
- **Sublingual**
- **Submandibular**
 - Surgery
 - Systemic therapies for metastatic disease



Surgical Management



Neck nodes

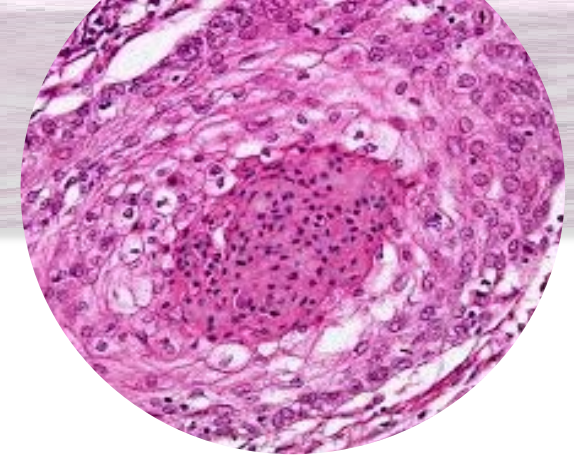
- Frequent metastasis into cervical nodes
- Negative impacts on survival and outcomes

Reconstruction

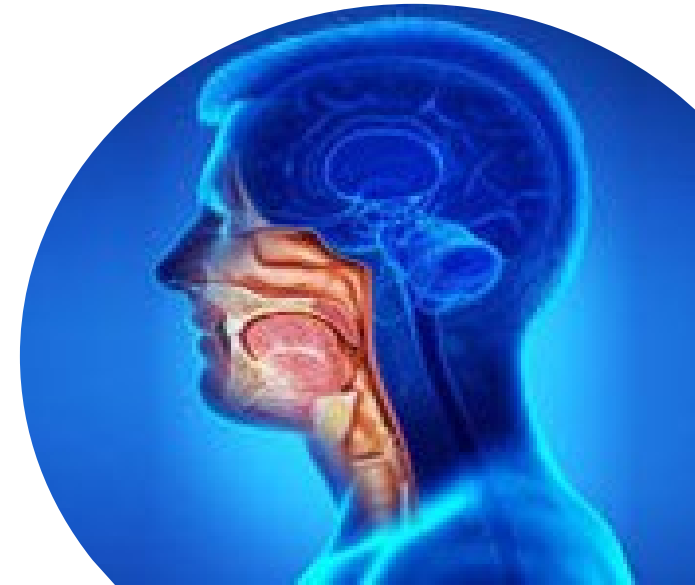
- Mandible
- Palate
- Larynx



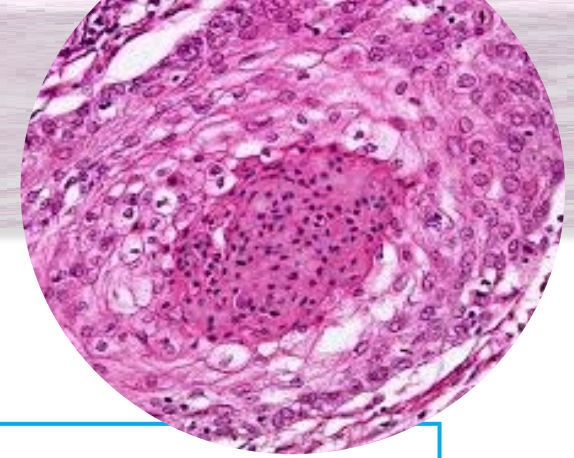
Complications



- **Functional alterations in surgery**
- **Treatment effects associated with CRT:**
 - mucositis, dermatitis, dysphagia
- **Delayed toxicities**
 - Radiation fibrosis syndrome
 - Dysphagia
 - Trismus
 - Osteoradionecrosis



Metastatic Disease



Poor prognosis

Median survival: 6-15 months

Systemic therapy mainstay

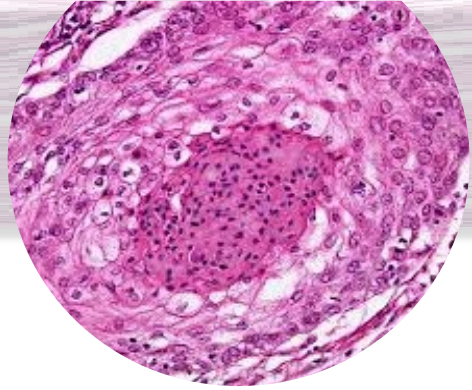
- PFS: 7-11 months
- OS: 14-18 months
 - Second-line therapies are less effective

Extensive supportive care needs



PFS = progression-free survival.

Lechner M, et al. *Nat Rev Clin Oncol*. 2022;19(5):306-327. Stenson KM, et al. UpToDate. Last updated June 28, 2024. Accessed October 31, 2024. <https://www.uptodate.com/contents/overview-of-the-diagnosis-and-staging-of-head-and-neck-cancer>.



Metastatic Disease

Management Considerations

Clinical Factors

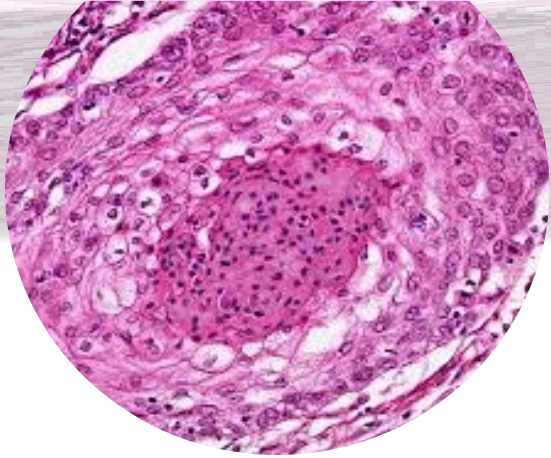
- Comorbidities
- Performance Status (PS)
- Prior therapy (surgery, chemo, RT)
- Pathological features: PD-L1, EGFR

Other Considerations

- ❖ Oligometastatic disease
- ❖ Locally recurrent
- ❖ Prior therapy setting
- ❖ Time from definitive therapy
- ❖ HPV status
- ❖ Combined Positive Score(CPS):
Predictive Marker for Response
-Robust reproducible PD-L1 scoring method



Patient Outcomes



Poor Outcomes
associated with

Active
smoking

Poor
Performance
Status (PS)

Significant
comorbidities

Prior RT

Weight loss



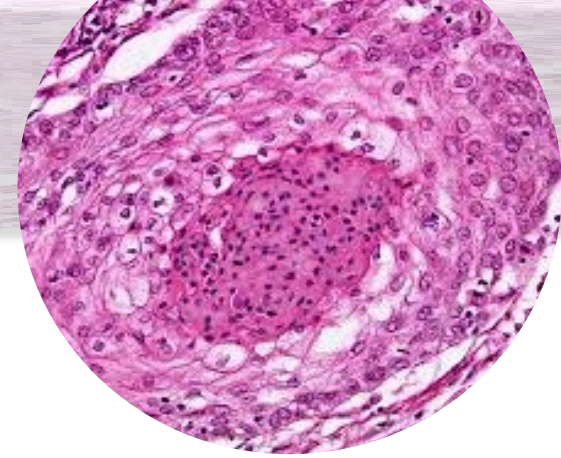
Management Strategies



Significant
improvement

- Surgical techniques
- Advancements in RT
- Reduced treatment-related toxicities
- Improvements in outcomes
- Historically, OS better in cisplatin + RT

Platinum-Eligible Patients



Current Management Strategies



High-dose cisplatin + RT



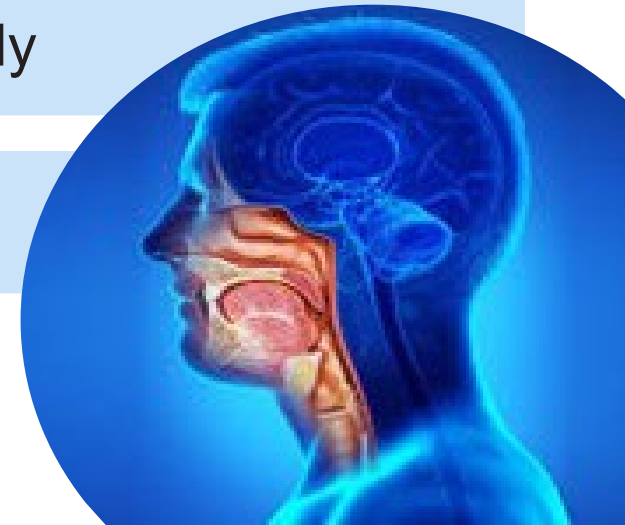
Low-dose cisplatin + RT



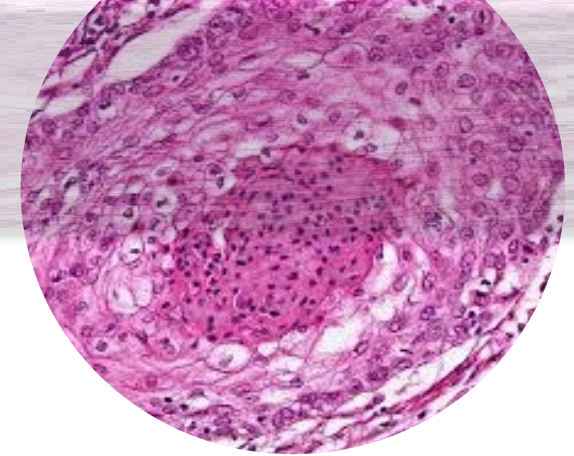
Benefit of systemic therapy decreases with age: MACH-NC study



Low-risk patients (exception: nasopharynx cancer)



Platinum-Ineligible Patients



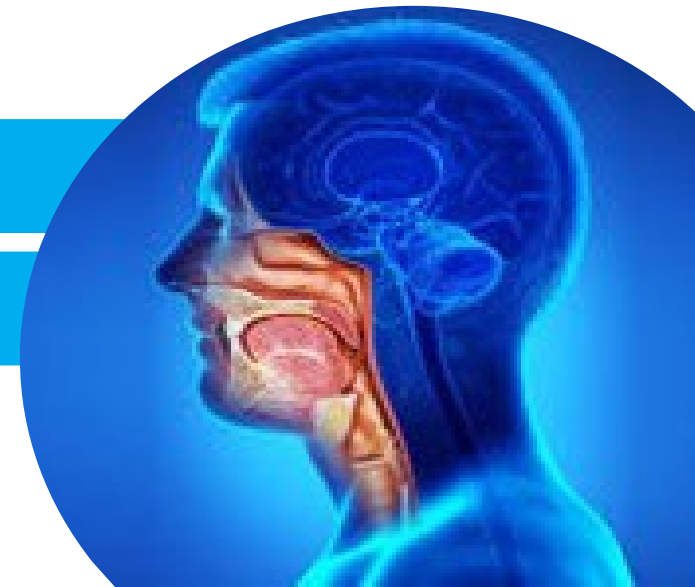
Patient Management Strategies

Absolute contraindication to cisplatin

- Poor renal function: CrCl <50-60 mL
- Baseline hearing loss
- Baseline neuropathies grade ≥ 2
- Hematologic toxicities
- Hypersensitivity
- CD4 <200 μl

Age >70

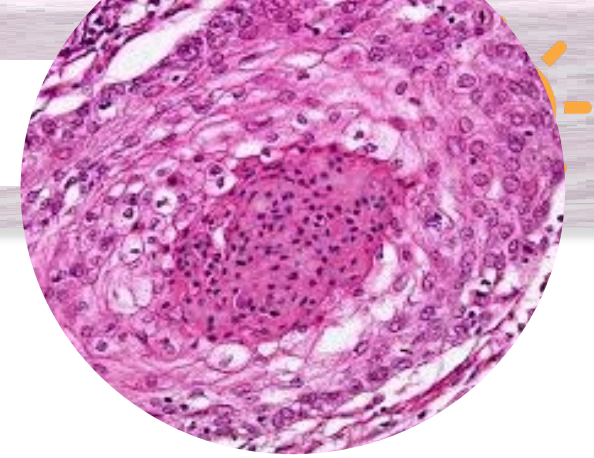
Comorbidities



CrCl = creatinine clearance.

Michelon I, et al. *J Cancer Res Clin Oncol*. 2024;150(8):379.

Platinum-Ineligible Patients



Therapeutic Treatment Options

Docetaxel plus cetuximab plus RT

Docetaxel + PORT

Low-dose cisplatin + RT

Cetuximab (EGFR inhibitor) + RT

Carboplatin/5FU

Carboplatin/paclitaxel

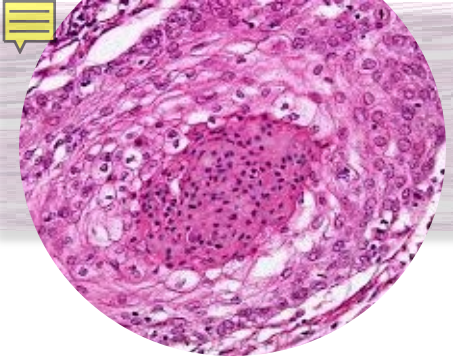
High Failure Rates



PORT = postoperative radiation treatment; 5FU = fluorouracil.

Kim SS, et al. *Curr Treat Options Oncol.* 2023;24(3):147-161. Haddad RI, et al. *Cancer Treat Rev.* 2023;119:102585.

NCCN. Last updated May 2024. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck_blocks.pdf.



Emerging Treatment Options for LA SCCHN

- **Targeted therapies**

- **Peposertib**- DNA-dependent protein kinase (DNA-PK) inhibitor

- **Immunotherapies**

- **Immune checkpoint inhibitors**

Studies evaluating ICI with RT in the definitive setting

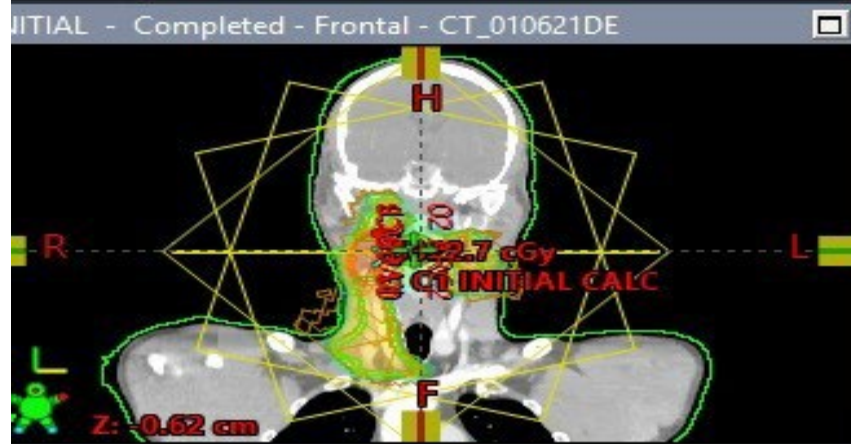
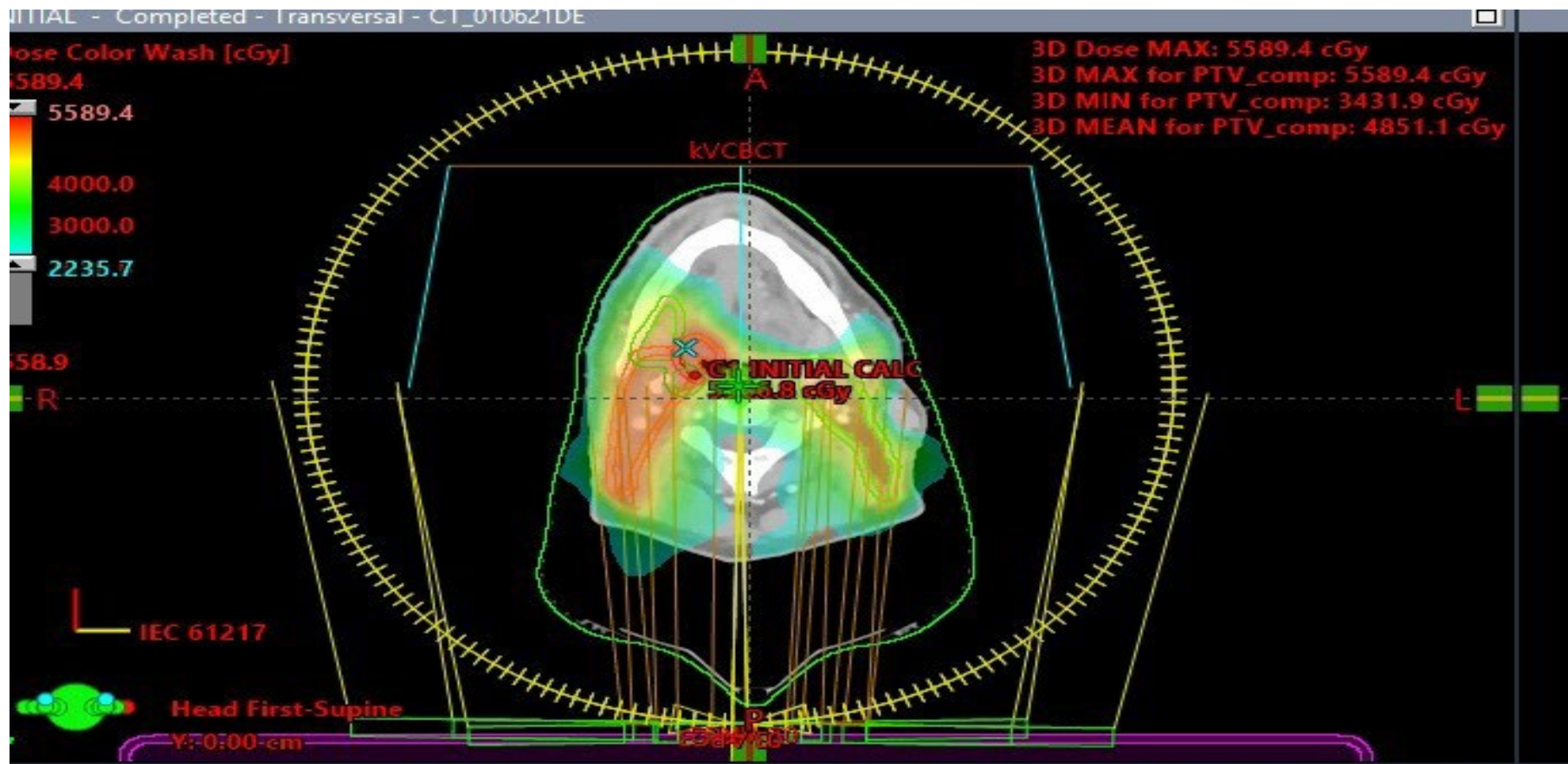














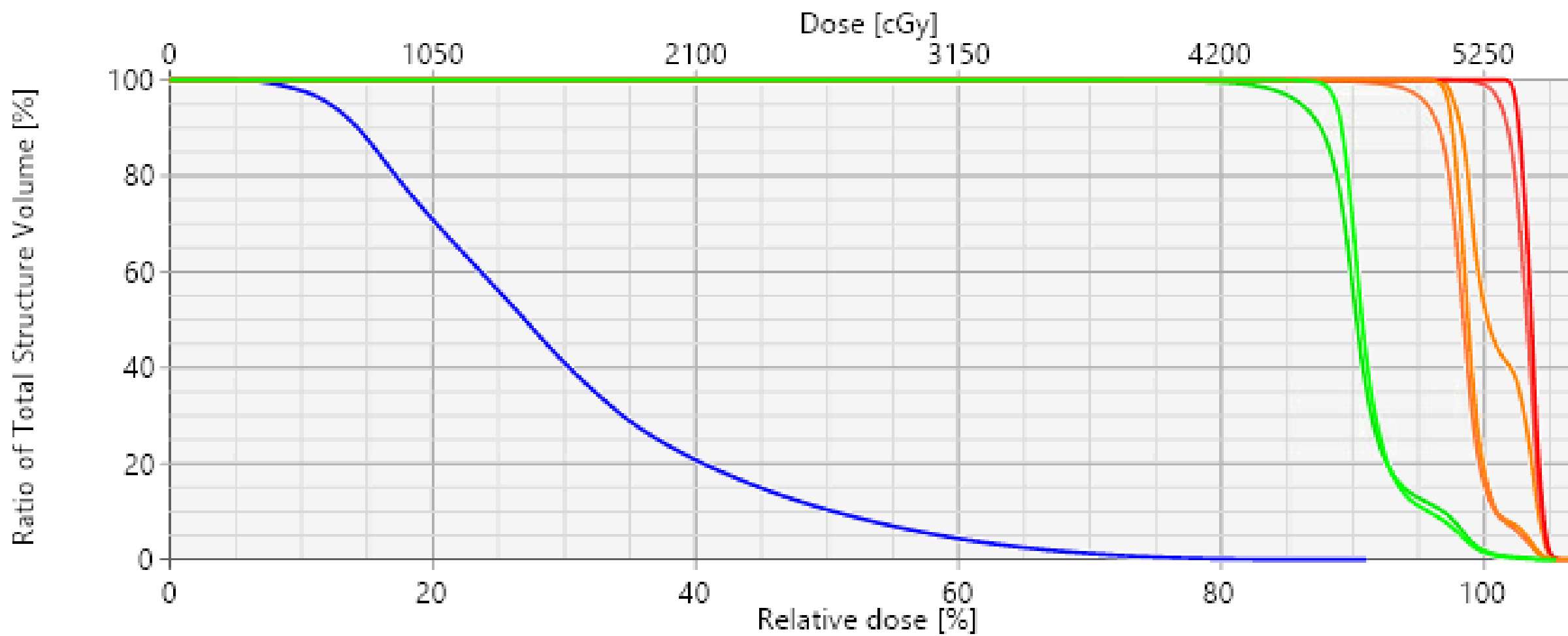




Fields | Dose | Reference Points | **Dose Statistics**

Show DVH	Show DVHE	Structure	Approval Status	Plan	Course	Volume [cm ³]	Dose Cover. [%]	Sampling Cover. [%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]	
<input checked="" type="checkbox"/>		CTV_4500	Approved	INITIAL	C1 H&N	147.9	100.0	100.0	4210.6	5545.7	4804.7	<input type="checkbox"/>
<input checked="" type="checkbox"/>		CTV_5000	Approved	INITIAL	C1 H&N	54.5	100.0	100.0	5015.0	5589.4	5204.0	<input type="checkbox"/>
<input checked="" type="checkbox"/>		CTV_5250	Approved	INITIAL	C1 H&N	2.4	100.0	99.9	5333.7	5552.8	5437.7	<input type="checkbox"/>
<input checked="" type="checkbox"/>		HRCTV_primary	Approved	INITIAL	C1 H&N	9.0	100.0	100.0	5045.2	5589.4	5301.2	<input type="checkbox"/>
<input checked="" type="checkbox"/>		PTV_4500	Approved	INITIAL	C1 H&N	289.6	100.0	100.0	3431.9	5545.7	4772.5	<input type="checkbox"/>
<input checked="" type="checkbox"/>		PTV_5000	Approved	INITIAL	C1 H&N	101.6	100.0	100.0	4312.4	5589.4	5173.8	<input type="checkbox"/>
<input checked="" type="checkbox"/>		PTV_5250	Approved	INITIAL	C1 H&N	7.3	100.0	100.1	4981.7	5563.9	5414.4	<input type="checkbox"/>
<input type="checkbox"/>		(D) BB	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input type="checkbox"/>		(D)heater45	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input type="checkbox"/>		(D)PTV45_opt	Approved	INITIAL	C1 H&N	244.0	100.0	100.0	3431.9	5343.3	4712.3	<input type="checkbox"/>
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<input type="checkbox"/>		(D)shoulder	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input type="checkbox"/>		BODY	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input type="checkbox"/>		Bone_Mandible	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input type="checkbox"/>		BoneMandible-PTV	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input type="checkbox"/>		BrainStem	Approved	INITIAL	C1 H&N							<input type="checkbox"/>
<input checked="" type="checkbox"/>		Cavity_Oral	Approved	INITIAL	C1 H&N	417.0	100.0	100.0	214.5	4781.4	1560.1	<input type="checkbox"/>

Dose Volume Histogram



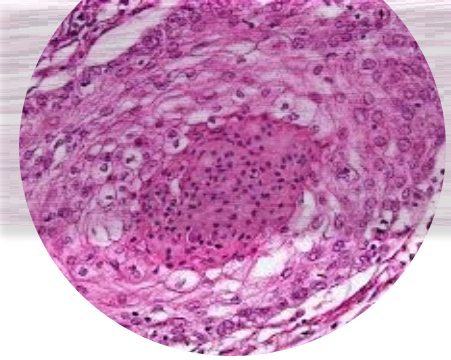
Role of the APP

- **Supportive role**
- **Survivorship care**
- **Management of chemotherapy and radiation effects**
 - Acute
 - Late
 - Chronic
- **Surgical effects: cosmetic alterations**
 - Lymphedema, dysphagia, cranial nerve dysfunction, or dental problems

APP = advanced practice provider.

Stenson KM, et al. UpToDate. Last updated June 28, 2024. Accessed October 31, 2024.

<https://www.uptodate.com/contents/overview-of-the-diagnosis-and-staging-of-head-and-neck-cancer>.



Surveillance

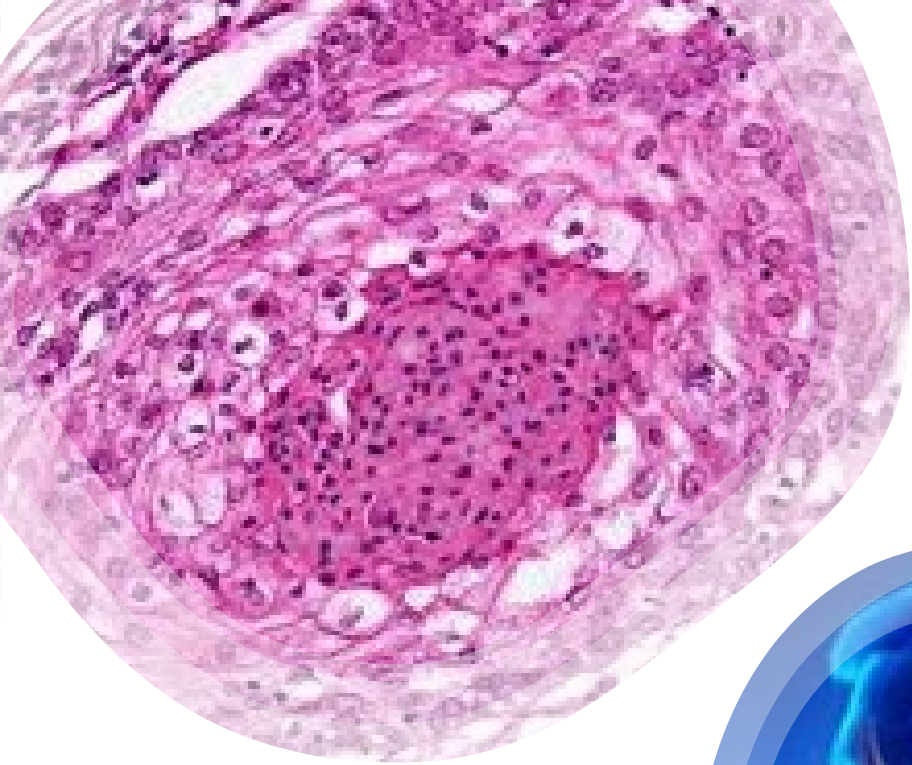
- **Reinforce importance of follow up:** PE and imaging
- **Locoregional recurrence**
- **Education:** signs and symptoms of second primary and/or recurrence
 - Weight loss
 - Lymphadenopathy
 - Dysphagia
- **Screen for psychosocial distress**
 - Anxiety
 - Financial toxicity
 - Fear
- **Survivorship care plan:** standards of the commission on cancer

PE = physical exam.

Stenson KM, et al. UpToDate. Last updated June 28, 2024. Accessed October 31, 2024.

<https://www.uptodate.com/contents/overview-of-the-diagnosis-and-staging-of-head-and-neck-cancer>.





Key Learning Points

- Approximately 60% of SCCHN cases are locally advanced at the time of diagnosis
- NCCN recommends docetaxel plus cetuximab plus RT for high-risk LA SCCHN in patients who are ineligible for cisplatin

Questions?