ARROCase
Nasopharynx Cancer

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Case: History

H&P:

- 37 yo male presents with left-sided neck mass, ear pressure, otalgia, and pain radiating down the ipsilateral neck.

- ROS:
  - + nose bleeds, numbness on the left cheek
  - - trismus, dysphagia, odynophagia, diplopia, or changes in vision

- Pertinent physical exam findings:
  - ECOG: (0) Fully active
  - HEENT: No mucosal lesions on direct/indirect examination. Poor dentition - no molars. **Perforated left TM** with erythematous auditory canal. Tenderness to palpation of the left post-auricular space.
  - Lymphatics: **Firm, matted adenopathy of the left level II-III nodes, with palpable ipsilateral supraclavicular nodes.**

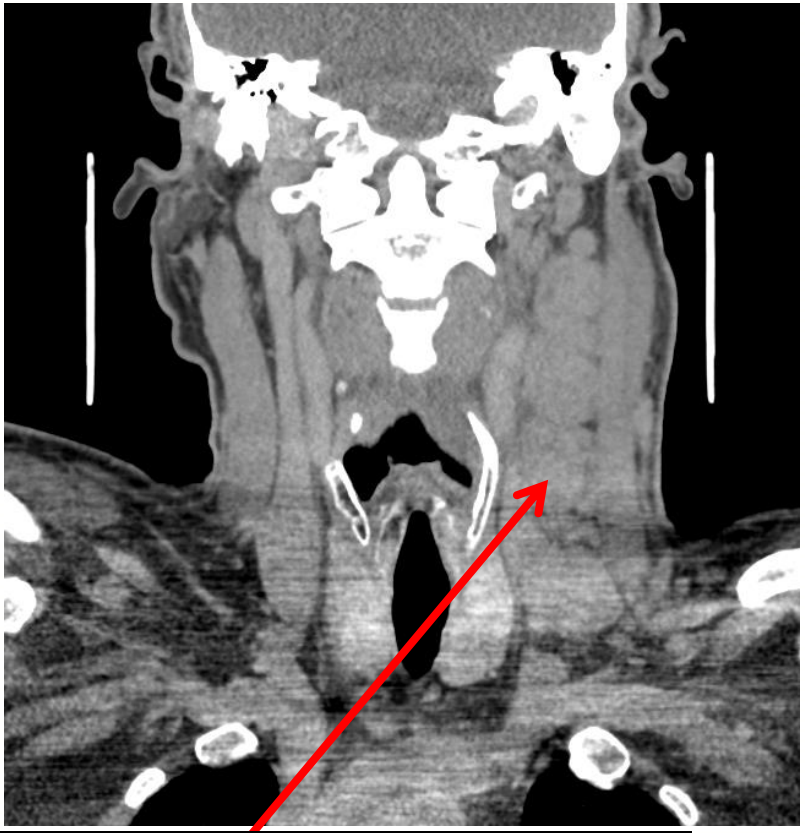
- Flexible nasal laryngoscopy: **ulcerated lesion of the left nasopharynx** obstructing the left Eustachian tube orifice, **fullness of the left fossa of rosenmuller**, extending toward the soft palate and posterior pharyngeal wall with partial obstruction of the pharynx.

Common presenting signs & symptoms

- Neck mass
- Epistaxis
- Middle ear effusion/otalgia/decreased hearing
- Headache/pain
- Nasal congestion and drainage
- Trismus
- Cranial nerve deficits
  - Petro-sphenoidal syndrome (CN III-IV, VI): Oculomotor signs/symptoms
  - Retro-parotidian syndrome (CN IV-XII): Enophthalmos, ptosis, miosis

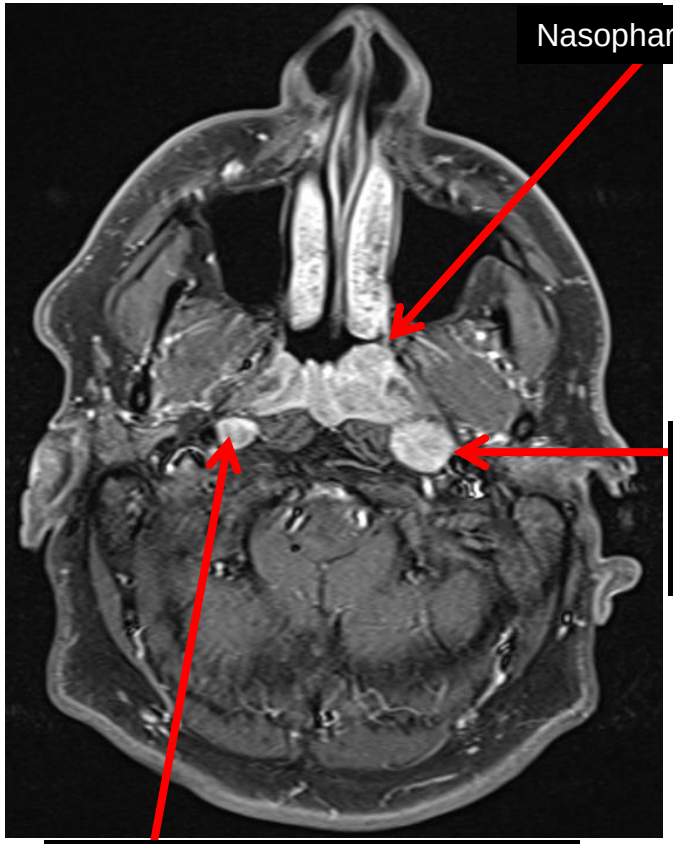
Case: Imaging

CT Neck



Multiple enlarged bilateral cervical lymph nodes (levels II – V), including supraclavicular node (level IV)

MRI Orbit, Face, & Neck



Work-Up & Evaluation[1]

- H&P including complete head & neck physical exam
  - Tobacco history
- Flexible nasopharyngeal fiber-optic laryngoscopy
- Labs
  - EBV titers
- Biopsy of the primary site or FNA of neck
- MRI w/ contrast – include skull base, nasopharynx, and neck to clavicles
- CT Neck & Chest, as clinically indicated
- PET-CT (especially for non-keratinizing histology, endemic phenotype, N2 or N3, and stage III – IV)
- Medical oncology consultation
- Dental evaluation
- Nutrition/GI evaluation
- Speech and swallow evaluation
- Audiology evaluation

Differential Diagnosis
of malignancy for nasopharyngeal mass

If small nasopharyngeal mass and confined to the mucosa:

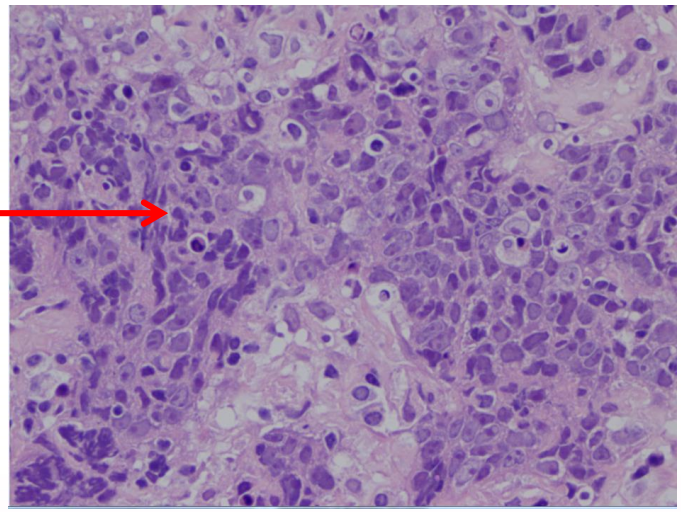
- Prominent, but normal adenoidal tissue
- Nasopharyngeal lymphoma
- Early primary nasopharyngeal malignancy

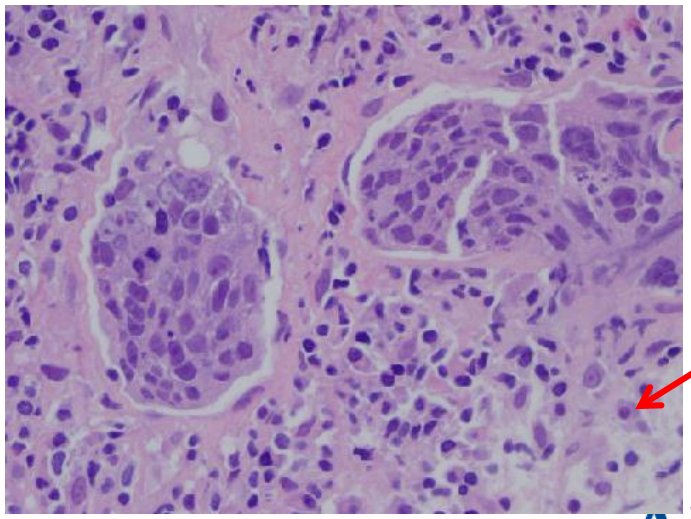
If larger nasopharyngeal mass +/- involvement of the skull base:

- Primary nasopharyngeal malignancy
- Adenoid cystic carcinoma
- Papillary adenocarcinoma
- Melanoma
- Plasmacytoma
- Lymphoma
- Chordoma/Chondrosarcoma
- Meningioma
- Rhabdomyosarcoma/other sarcoma
- Metastases

Case: Pathology

- He underwent US-guided FNA of the left cervical neck mass
- Pathology: poorly differentiated carcinoma
  - Pleomorphic epithelioid cells in a background of lymphocytes
  - + cytokeratin
  - p16 negative
  - EBV in-situ hybridization negative
  - Neuron specific enolase negative





Nasopharynx Cancer

Incidence:

- 5 per 1 million in the USA
- 100 – 400 per 1 million in Asia/Africa

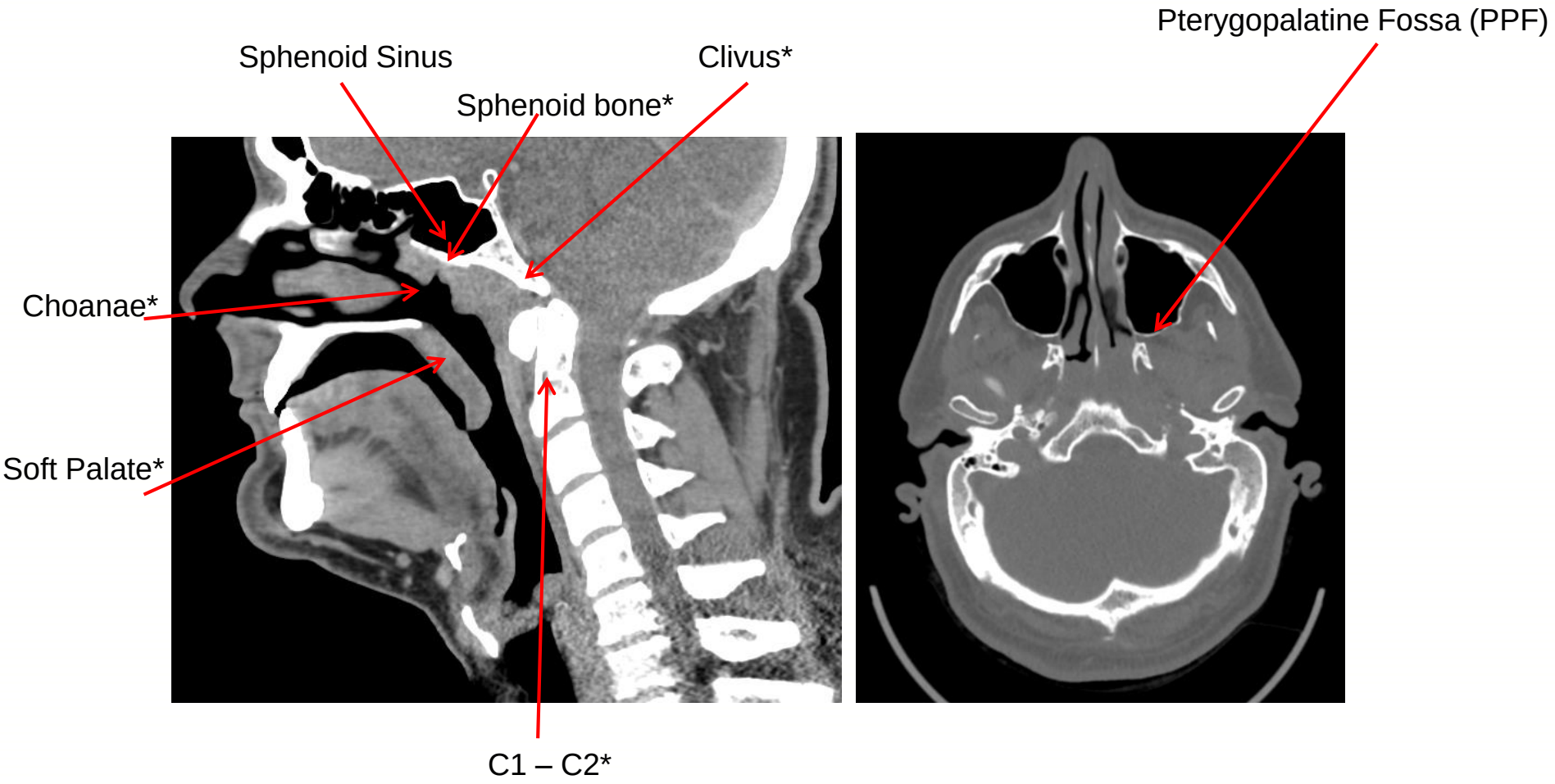
Risk Factors:

- Salted or pickled foods
- Metal dust
- Epstein-Barr virus (EBV)
- Smoking
- HLA/Genetic

Presenting signs/symptoms:

- Palpable cervical adenopathy
  - 70% cN+
  - 90% pN+ (50% bilateral)
- Nasal discharge
- Hearing loss
- Trismus
- Cranial neuropathy (CN II – XII)

Anatomy: Skull Base & Nasopharynx

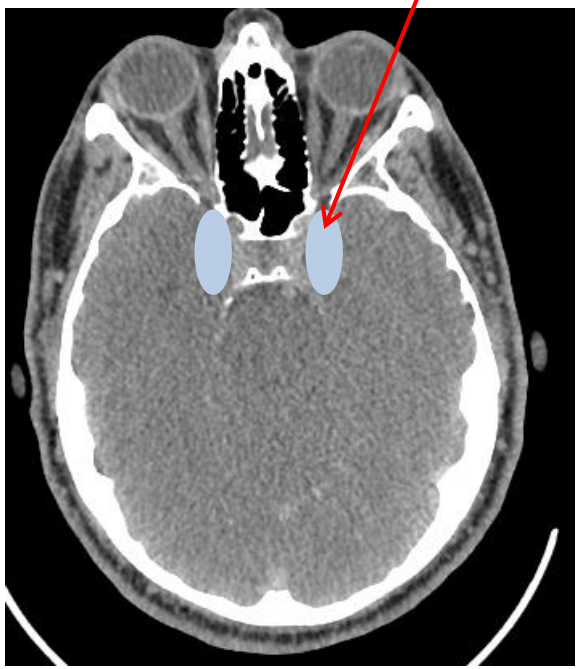


*anatomic boundaries of the NPx

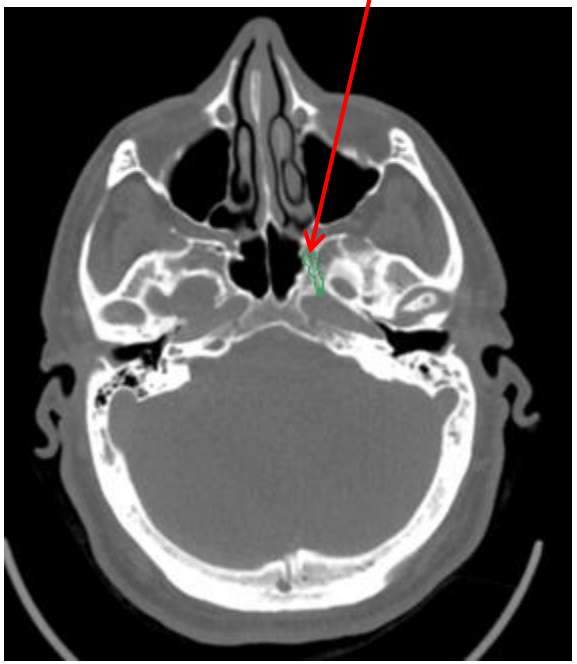
Anatomy: Skull Base & Nasopharynx

Parapharyngeal space

Cavernous sinus



Foramen rotundum



WHO Grading System Nasopharyngeal Carcinoma

- **WHO I: keratinizing squamous cell carcinoma**
  - 20% prevalence
  - Associated with smoking, HPV
  - Poor LC
  - Lower risk of DM

- **WHO II: non-keratinizing, squamous cell carcinoma**
  - (A) Differentiated type
  - (B) Undifferentiated type
  - 30 – 40% prevalence

- **WHO III: undifferentiated, lympho-epithelial, or basaloid squamous cell carcinoma**
  - 40 – 50% prevalence
  - Most strongly associated with EBV
  - Better LC
  - Higher risk of DM

AJCC Staging System[2] Nasopharyngeal Carcinoma

Tumor

T1: confined to NPx, OPx, and/or nasal cavity without parapharyngeal extension

T2: parapharyngeal extension

T3: bony structures of skull case of paranasal sinuses

T4: intra-cranial extension, cranial nerves, HPx, orbit, or with extension to infra-temporal fossa/masticator space

Nodes

N1: unilateral, ≤ 6 cm, above SCLV fossa; or uni/bilateral RP nodes, ≤ 6 cm

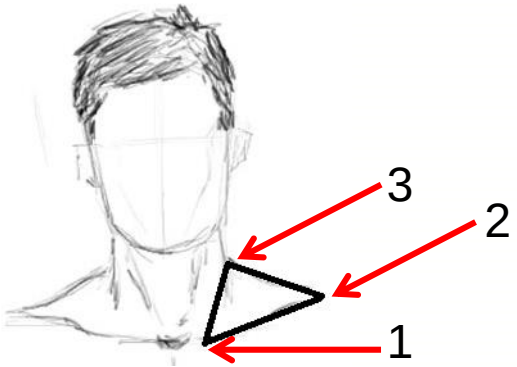
N2: bilateral, ≤ 6 cm, above SCLV fossa

N3a: > 6cm

N3b: SCLV fossa*

Metastases

M1: any distant metastasis



**SCLV fossa is the triangular region defined by the 3 points:*

(1) Superior margin of the sternal end of clavicle

(2) Superior margin of lateral end of clavicle

(3) Point where neck meets shoulder

Abbreviations:

NPx: nasopharynx, OPx: oropharynx, HPx: hypopharynx, SCLV: supraclavicular

AJCC Staging System[2] Nasopharyngeal Carcinoma

	T1	T2	T3	T4
N0	I	II	III	IVA
N1	II	II	III	IVA
N2	III	III	III	IVA
N3	IVB	IVB	IVB	IVB
M1	IVC	IVC	IVC	IVC

Case: Management

- cT1 cN3b cM0, stage IVB, p16- EBV- poorly differentiated nasopharyngeal carcinoma

- Consultation with Otolaryngology, Medical Oncology, Radiation Oncology

- Treatment options for T2-4 or N+ include:
  - Concurrent chemoradiation → +/- adjuvant chemo
  - Induction chemo → concurrent chemoradiation

Case: Management

- This patient received:
  - Concurrent CRT to 70 Gy in 33 fractions with weekly cisplatin 40 mg/m^2
  - Adjuvant/consolidation cisplatin/5-FU

Radiation Planning

- Simulation:
  - Supine, long mask, IV contrast:
  - Co-register with MRI +/- PET-CT

- Radiation Dose/Fractionation:
  - PTV1: 69.96 Gy in 33 fractions (2.12 Gy/Fx)
  - PTV2: 59.4 Gy in 33 fractions (1.8 Gy/Fx)
  - PTV3: 54 Gy in 33 fractions (1.63 Gy/Fx)
  - Consider hyper-fractionation if dose to optic structures/brainstem would be otherwise unacceptable

Radiation Technique

- IMRT
- Proton beam radiotherapy
- Brachytherapy
  - Intracavitary boost
  - Consider for recurrent disease
  - Possible dose escalation of early/advanced primary tumors

Radiation Contouring

- PTV1 (69.96 Gy)
  - Gross disease
- PTV2 (59.4 Gy)
  - High risk subclinical disease:
    - Sphenoid sinus
    - Cavernous sinus
    - Skull base
    - Clivus
    - Posterior 1/3 of maxillary sinus
    - Posterior 1/3 of nasal cavity
    - Pterygopalatine fossae
    - Parapharyngeal space
    - Retropharyngeal space
    - Soft palate
- PTV3 (54 Gy):
  - Elective nodal coverage:
    - Retrostyloid space
    - Bilateral IB – V (can omit IB, if N0)

Contouring references:

- e-contour http://econtour.org/cases/2
- http://www.nyp.org/pdf/imrt_2010_talk2_lee.pdf

Dose Constraints[3]

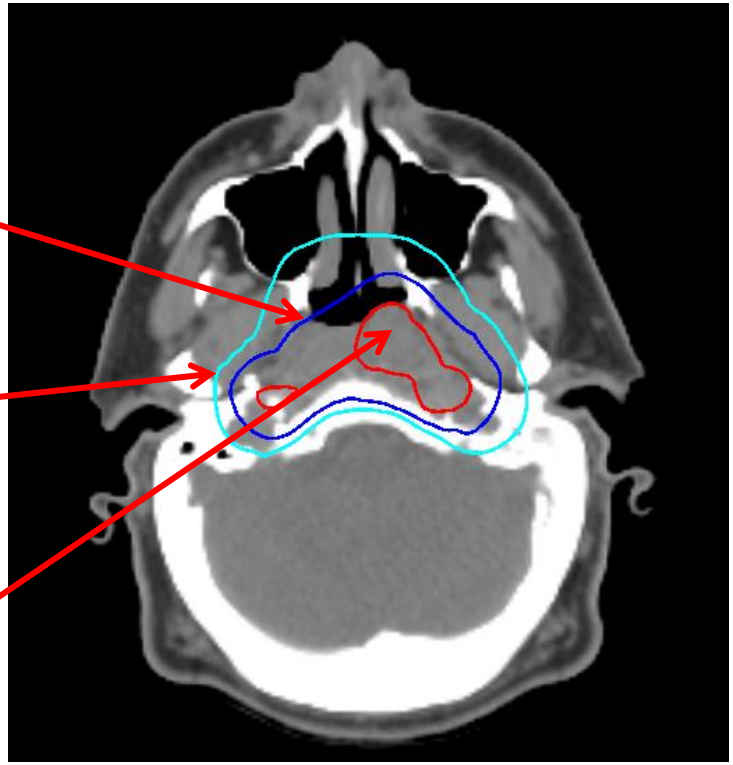
Critical normal structures (higher priority):

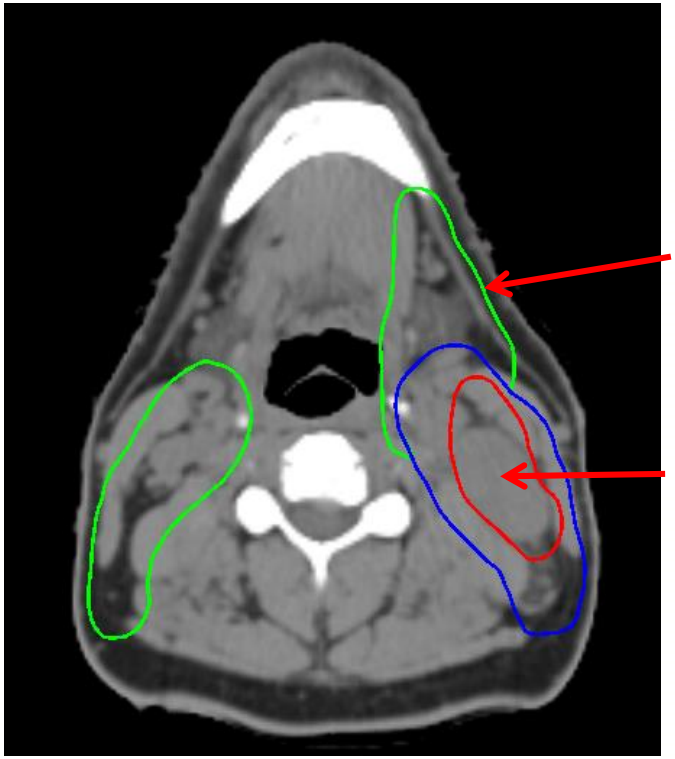
• Brainstem, optic nerves, chiasm	Max < 54 Gy
• Spinal cord	Max < 45 Gy
• Mandible/TMJ	Max < 70 Gy
• Temporal lobes	Max < 60 Gy

Other normal structures (lower priority):

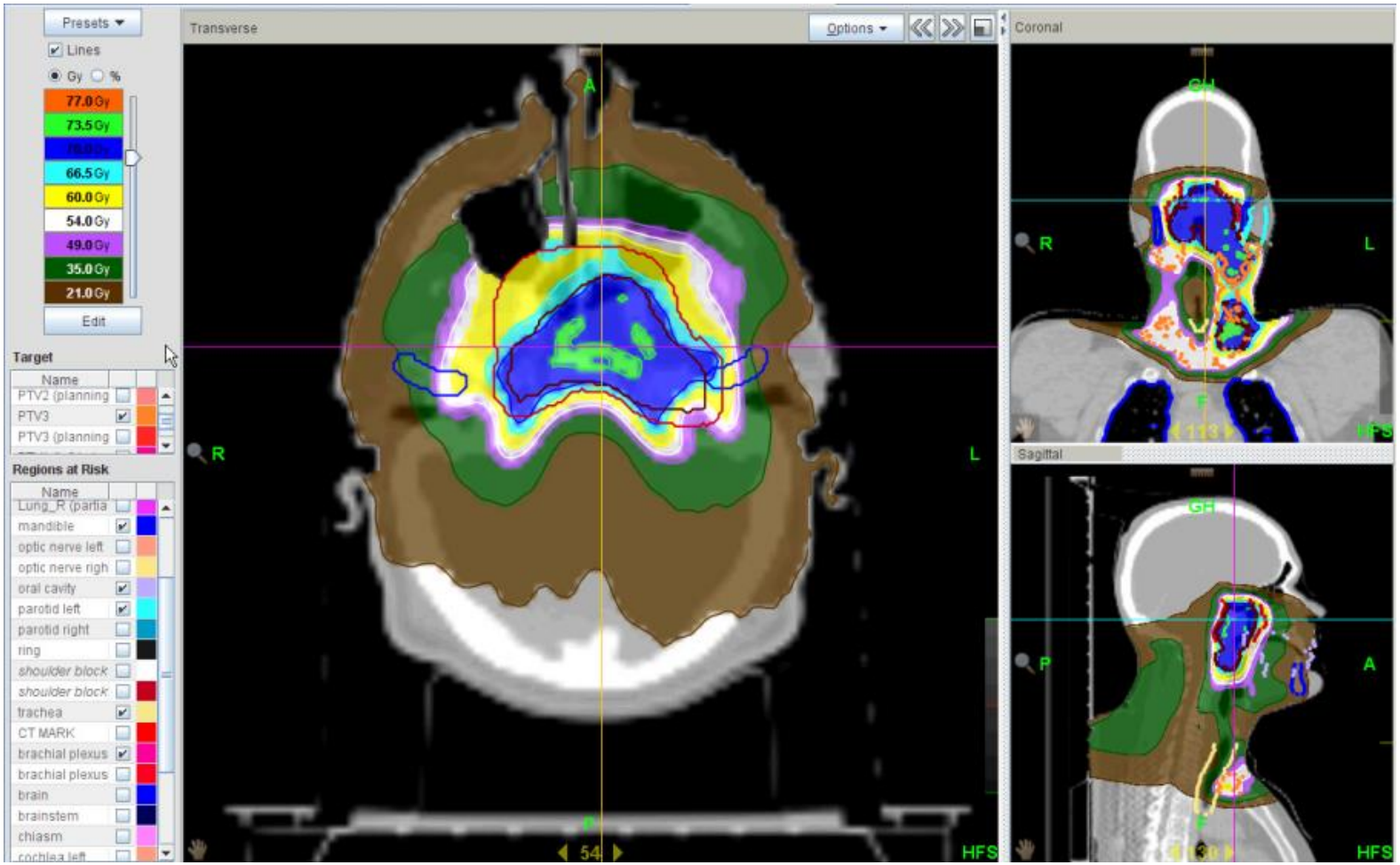
• Parotid glands	Mean ≤ 26 Gy in at least one gland, or at least 20 cc of the combined volume of both parotid glands to receive < 20 Gy, or at least 50% of one gland to receive < 30 Gy
• Tongue	Max < 55 Gy
• Inner/middle ears (especially with concurrent Cisplatin)	Mean < 50 Gy
• Eyes	Mean < 35 Gy
• Glottic larynx	Mean < 45 Gy
• Lens	ALARA

Case: Target Volumes

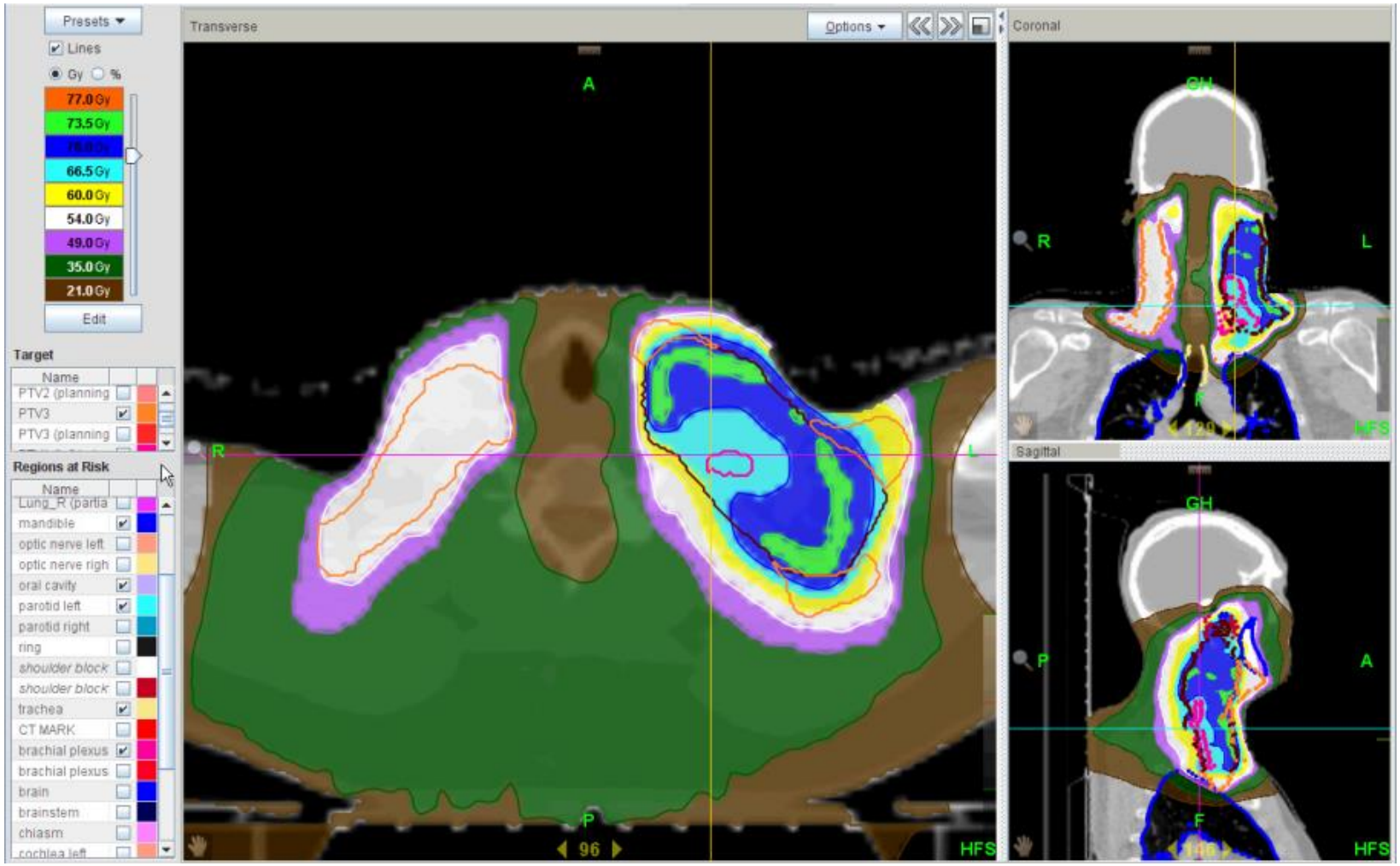




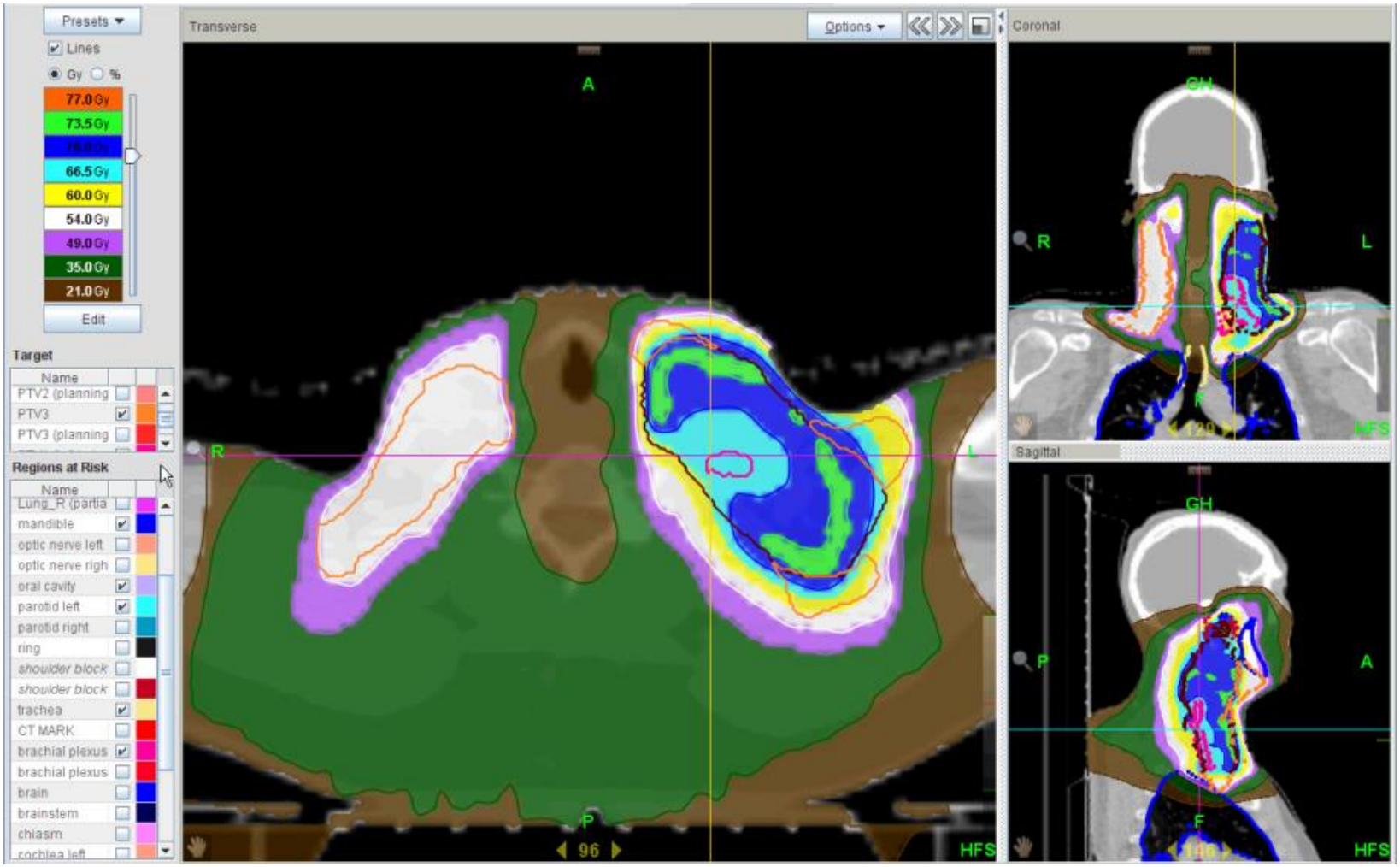
Case: Isodose Distribution



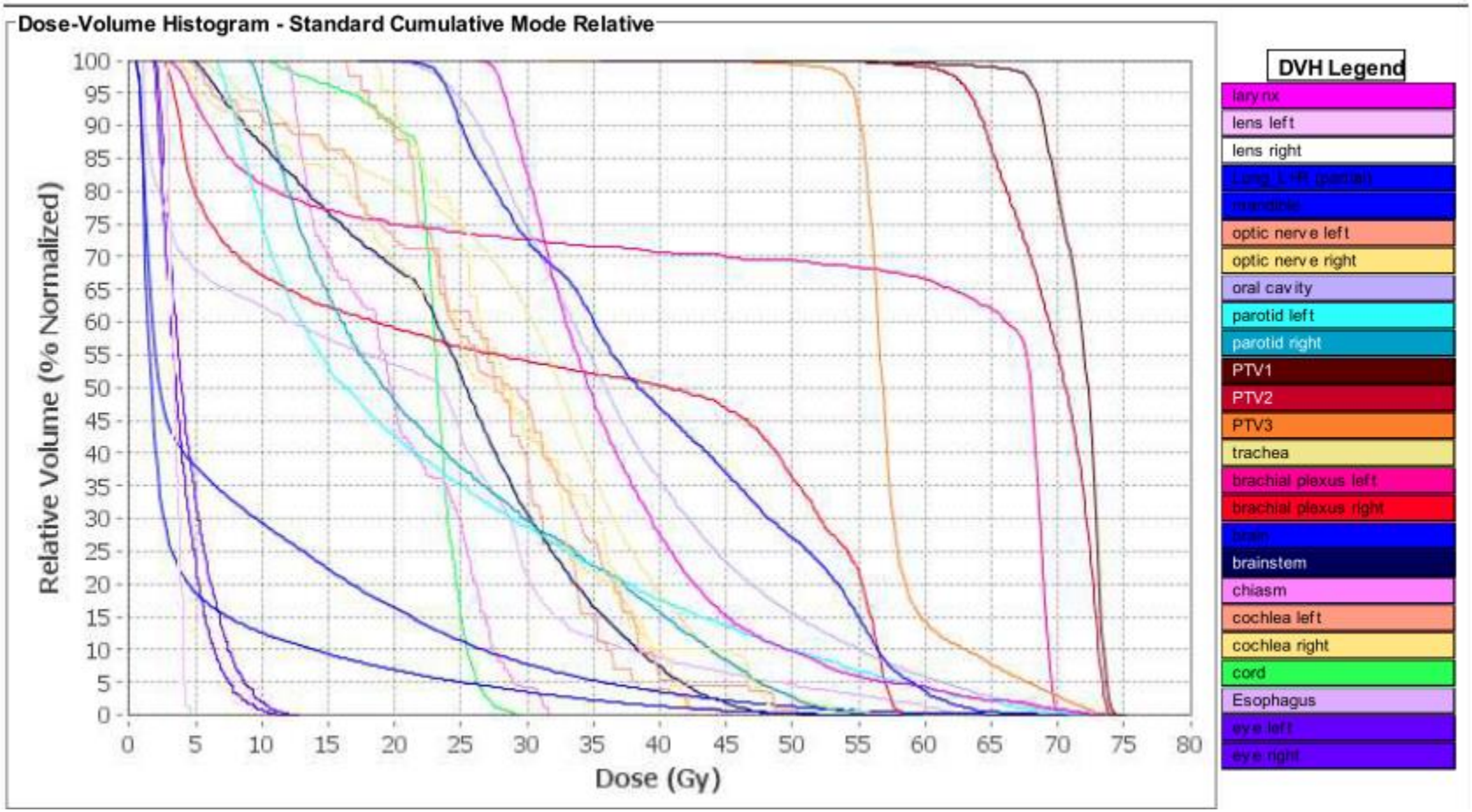
Case: Isodose Distribution



Case: Isodose Distribution



Case: Dose Volume Histogram



Treatment Algorithm

Stage	Treatment options
T1 N0	• Definitive RT
T1 N+ T2-4 N0 T2-4 N+	• Concurrent CRT → +/- adjuvant chemo • Induction chemo → concurrent CRT
Tx Nx M1	• Chemotherapy (platinum-based) • Concurrent CRT

Chemotherapy

Evidence for Concurrent + Adjuvant[4-6]

	Intergroup 0099 ***Al Sarraf et al., JCO 1998***	**RTOG 0225** ***Lee et al., JCO 2009***
Design	Randomized, phase III	Phase II
# Patients	147	68
Treatment	RT alone vs. CRT	RT +/- Chemo (for ≥T2 and/or N+)
Radiation	Primary tumor: 70 Gy Lymph nodes N0: 50 Gy N+ ≤2cm: 66 Gy N+ >2cm: 70 Gy	Primary Tumor: 70 Gy at 2.12 Gy/Fx Intermediate risk: 59.4 Gy at 1.8 Gy/Fx
Chemotherapy	Concurrent: cisplatin 100 mg/m^2 q3weeks Adjuvant: cisplatin 80 mg/m^2 + 5-FU 100 mg/m2/day q4weeks x 4	Concurrent: cisplatin 100 mg/m^2 q3weeks Adjuvant: cisplatin 80 mg/m^2 + 5-FU 100 mg/m2/day q4weeks x 4
Outcomes	3-year PFS: 24 → 69% ($p < .001$) 3-year OS: 46 → 76% ($p < .001$)	2-year PFS: 72.7% 2-year OS: 80.2%
Comments	Large # of WHO type I RT alone arm performed poorly Closed early due to SS improved survival with chemo	94% WHO types II – III IMRT is feasible No excessive toxicity

- Results of Intergroup 0099 study confirmed by Chan *et al.* CRT with weekly cisplatin vs. RT alone led to 5-year OS improvement 59 → 70%

Chemotherapy

Evidence for Induction:

- No demonstrated benefit of induction chemo
- NCCN Guidelines category 3 recommendation

Evidence for Adjuvant[7]:

- No demonstrated benefit for adjuvant chemo following definitive RT or CRT, although long term data not yet available
- NCCN Guidelines category 2B recommendation

Follow Up for Nasopharyngeal Cancer

- H&P + complete H&N physical exam +/- mirror/fiberoptic exam
  - q1-3 months for year 1
  - q2-6 months for year 2
  - q4-8 months for years 3 – 5
  - Yearly for years > 5

- Imaging for signs/symptoms
- TSH yearly (if irradiated)
- Speech/swallowing/dental/hearing evaluations
- Consider EBV-DNA monitoring

Nasopharynx Clinical Pearls

- Uncommon in the United States
- High likelihood of distant metastases
- Rarely, parotid nodal relapses can occur
- Due to the anatomic location, RT traditionally used over surgery
- Local control with RT alone of early (T1 – T2) tumors 80 – 90%
- Local control with RT alone of T3 – T4 tumors 30 – 65%
- Concurrent cisplatin-based chemo + RT has been shown to improve OS
- No evidence to support induction chemotherapy
- Little evidence to support adjuvant chemotherapy, although awaiting further results of Chen *et al.* phase 3 randomized trial
- RT technique is IMRT with simultaneous integrated boosts to 70 Gy, 59.4 Gy, and 54 Gy

References

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