Locally Advanced Nasopharynx

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Case Presentation

- 74 yo male presents with 2 years of epistaxis and 3 month history of a right neck mass

- What would you like to do next?

History & Physical

- HPI:
  - local ENT had scoped him 2 years ago with no abnormal findings.
  - Reports he has had stable bloody nasal discharge for the past two years which worsened 6 mo prior.
  - Right neck mass grown over three months, non-tender
  - Congested bilaterally but worse on the right side
- PMH: CAD, UC in remission on mesalamine
- PFH: No hx of cancer
- Social hx: Lives in midwest, former smoker 1 pack/week quit 30 years prior, no etoh or drug use, retired carpet cleaner

History and Physical

- Physical exam focusing on **HEENT and Neuro Exam**
- HEENT:
  - NCAT. Sclera anicteric. PERRL. EOMI. No evident asymmetries, obvious scars, lesions or masses. Palpation of face did not reveal any sinus tenderness.
  - Ears: Otoscopic examination demonstrates external auditory canals are normal bilaterally. No effusions bilaterally.
  - Nose: Nasal mucosa is pink and the septum is deviated posteriorly to left, visualized turbinates are normal in appearance.
  - Oral cavity & oropharynx: lips and gums normal, oral and pharyngeal mucosa moist, palate elevates normally, tongue mobile and without palpable lesions, tonsils without masses
  - Trismus: none
  - Dentition: poor
- Neck: Normal ROM. A **~2cm palpable right level IIb mass**. No left palpable LAD no supraclavicular LAD.
- Neuro: Strength intact and symmetric. Sensation intact. CN II-XII intact. Gait normal. No focal deficits. No pain with EOMI
- Skin: No rashes noted

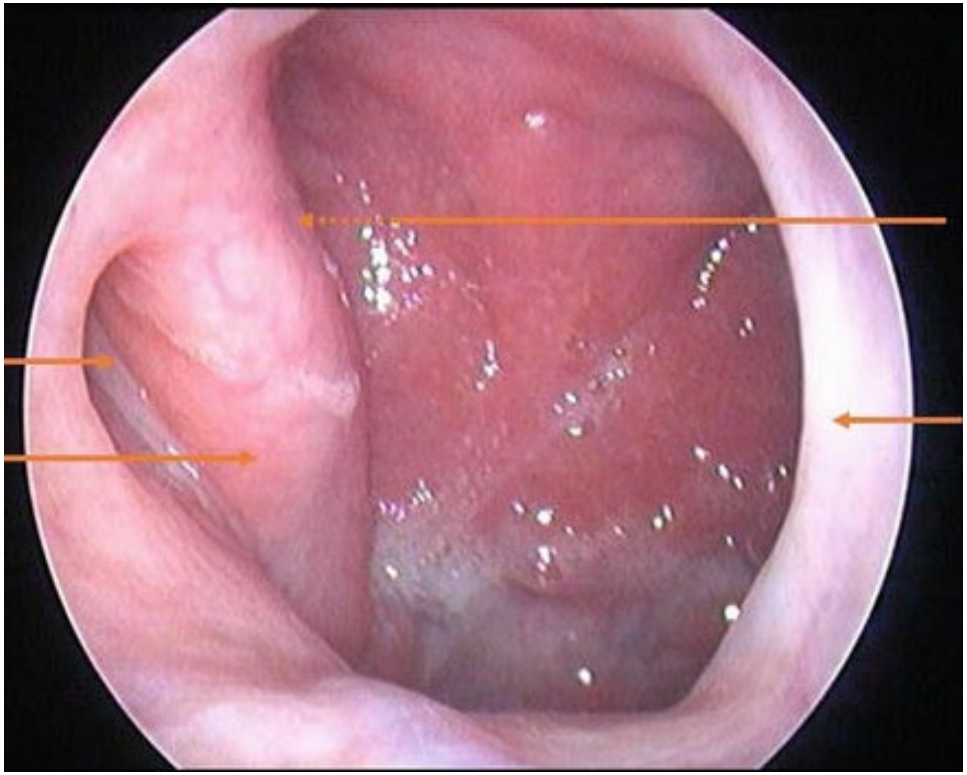
Next step?

Next step?

- Flexible nasopharyngolaryngoscopy

- Bilateral nasal cavities were unremarkable. **There was a nasopharyngeal mass with erosion on the right and extending to the left.** The oropharynx was without masses or lesions. The base of tongue showed no gross lesions. The hypopharynx including the pyriform sinuses were normal. The supraglottis was unremarkable, with no edema of the false vocal folds. The larynx itself showed no lesions. , including the arytenoids, aryepiglottic folds, and true vocal folds bilaterally. The vocal folds moved well bilaterally. The immediate subglottic area was unremarkable, without concern for lesions, erythema, or stenosis.

Anatomy- identify the following:



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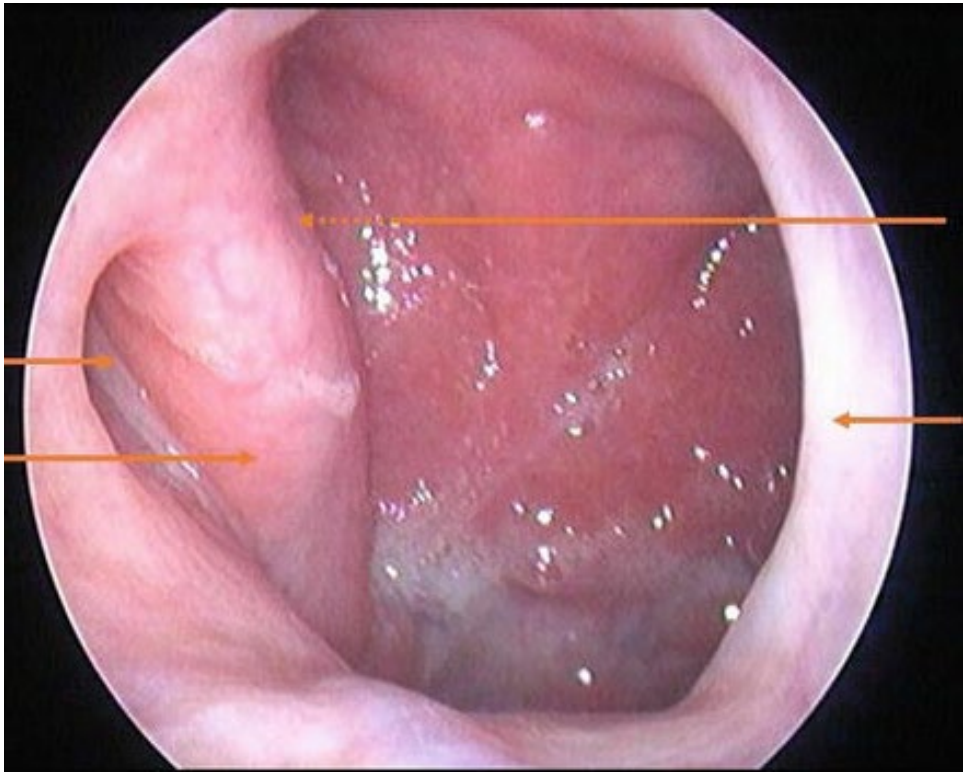


Differential

- Benign lesions
  - Polyposis, angiofibromas, polyps, papilloma, adenoid hypertrophy, cysts
- Malignancy
  - Nasopharyngeal carcinoma, lymphoma, sarcoma, mucosal melanomas
- Inflammatory conditions

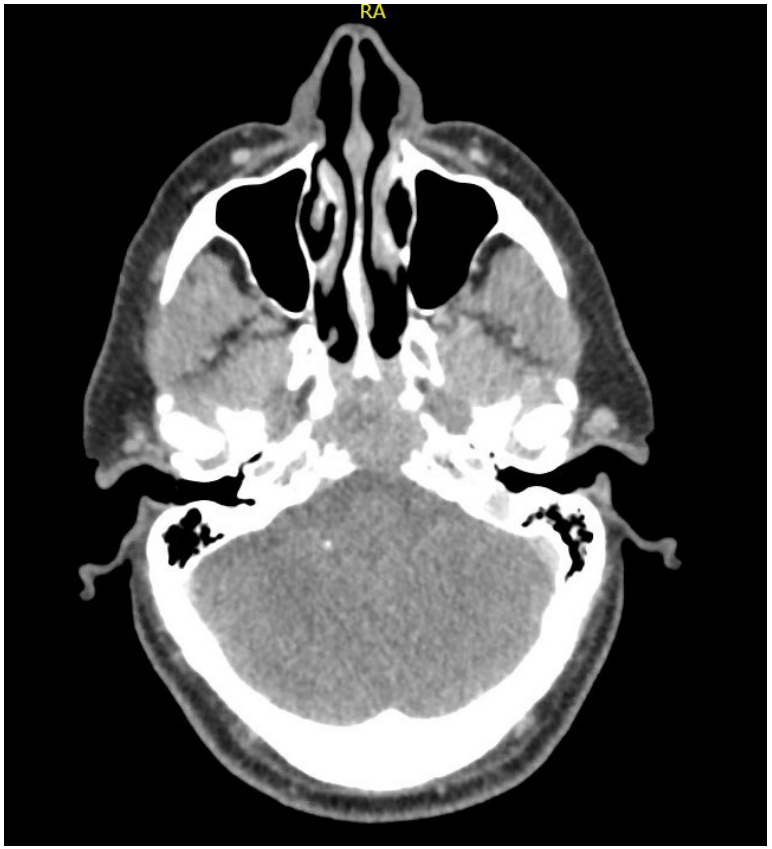
Next step?

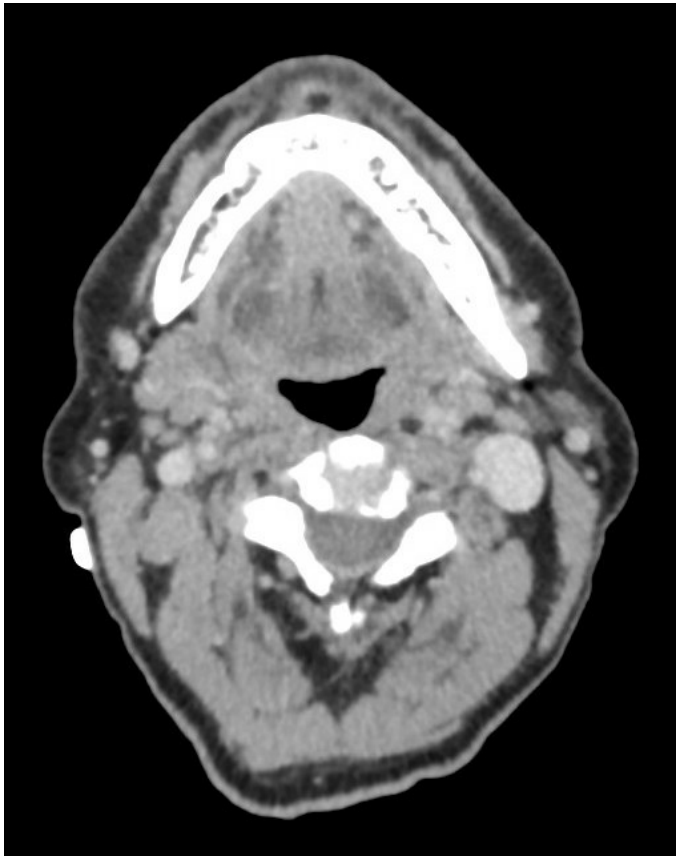
Next step?

- Imaging-
  - CT Neck with Contrast
  - MRI skull base w and w/o contrast

CT Neck with Contrast

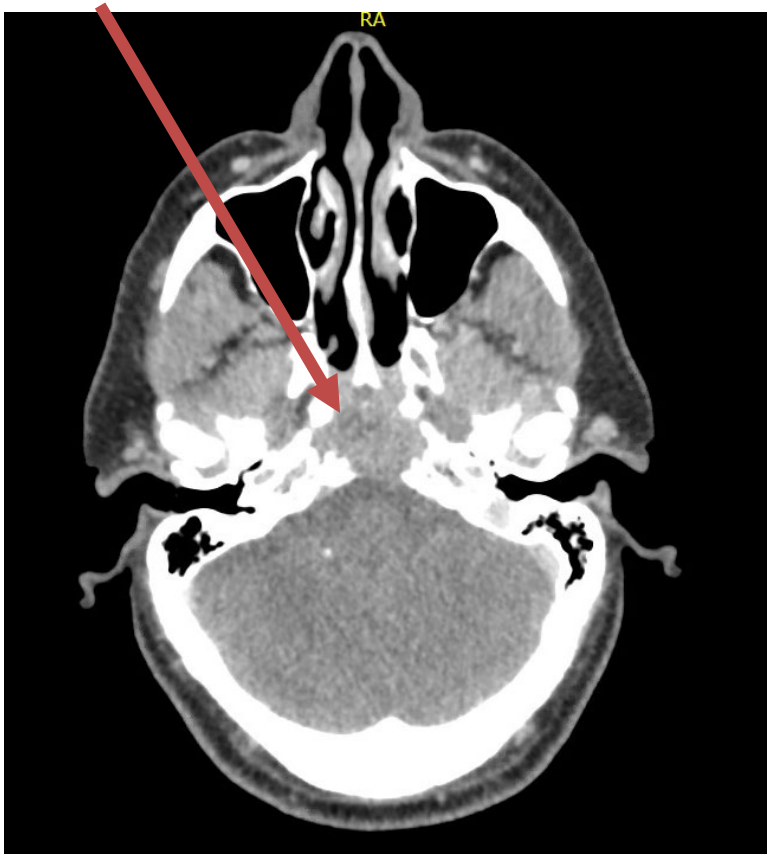
What do you see?



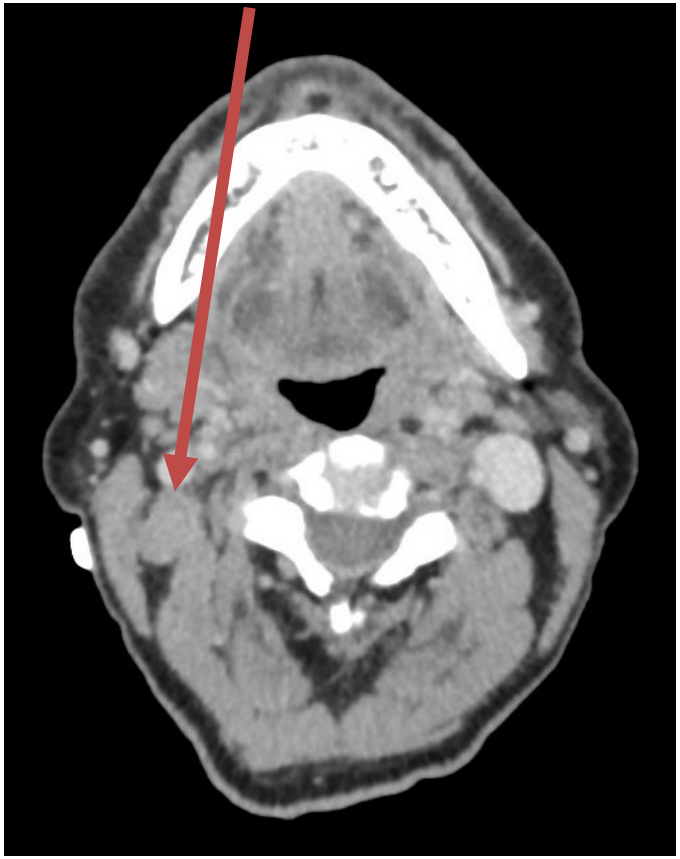


CT Neck with Contrast

Central nasopharynx with clival erosion

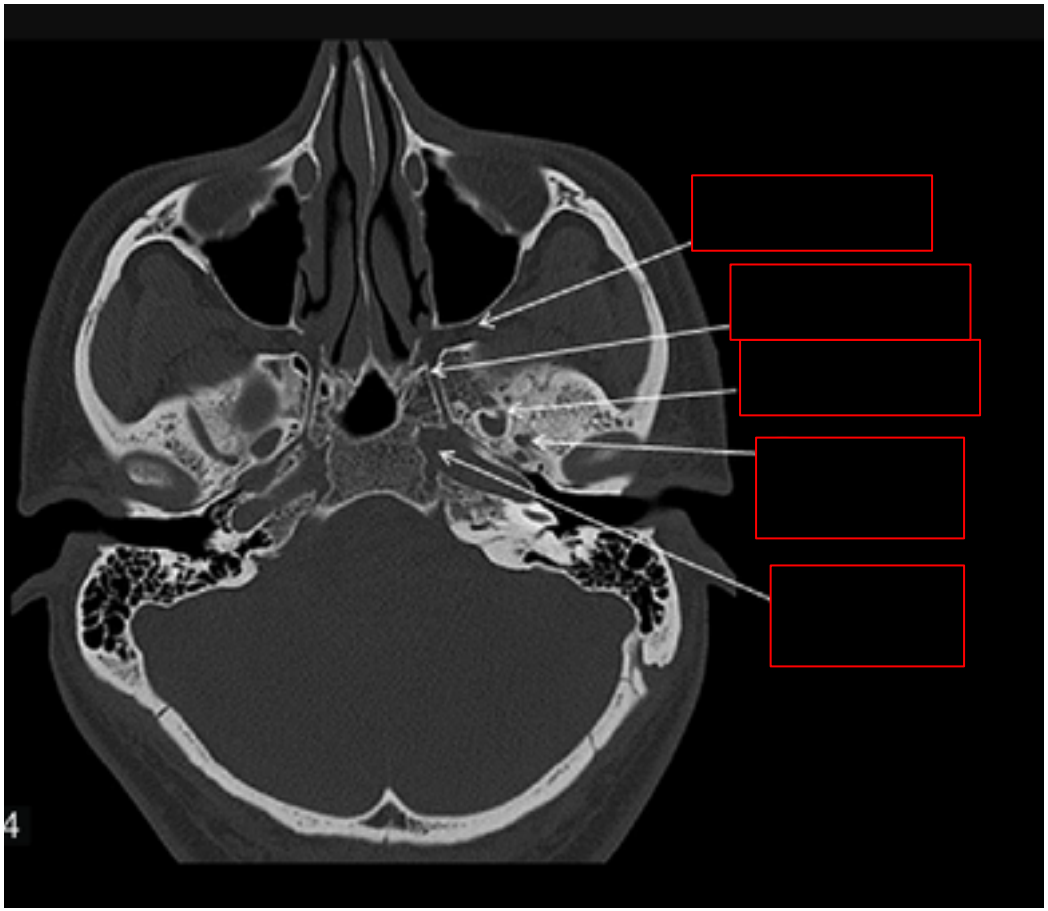


Right level 2 lymph node



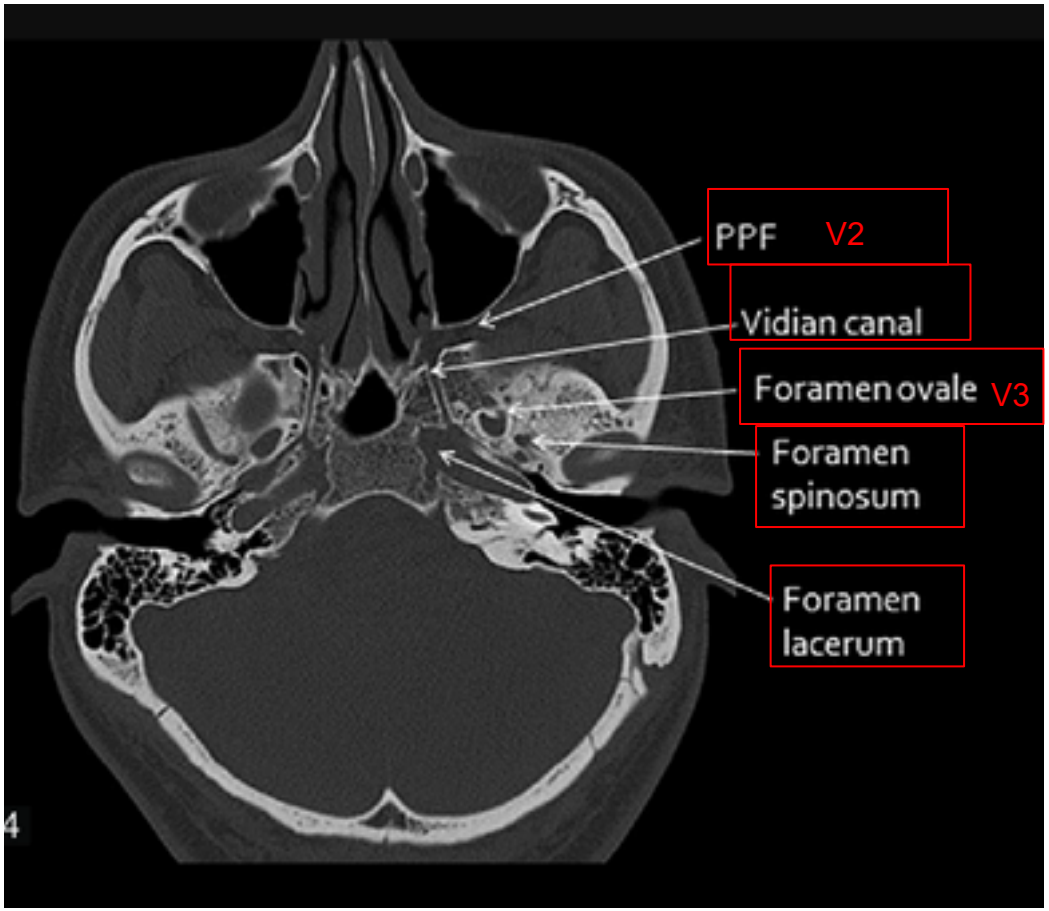
Skull base anatomy

Identify the red boxes and any pertinent nerves that traverse



Skull base anatomy

Identify the red boxes and any pertinent nerves that travel through the area



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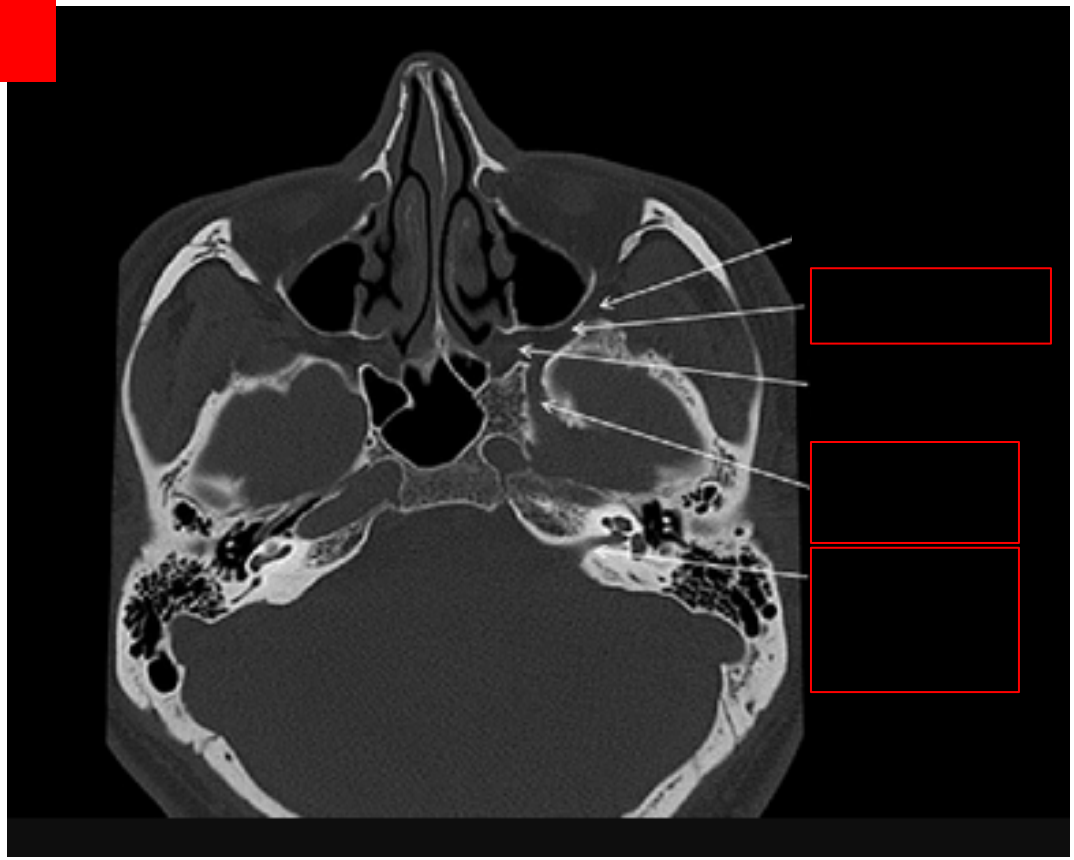

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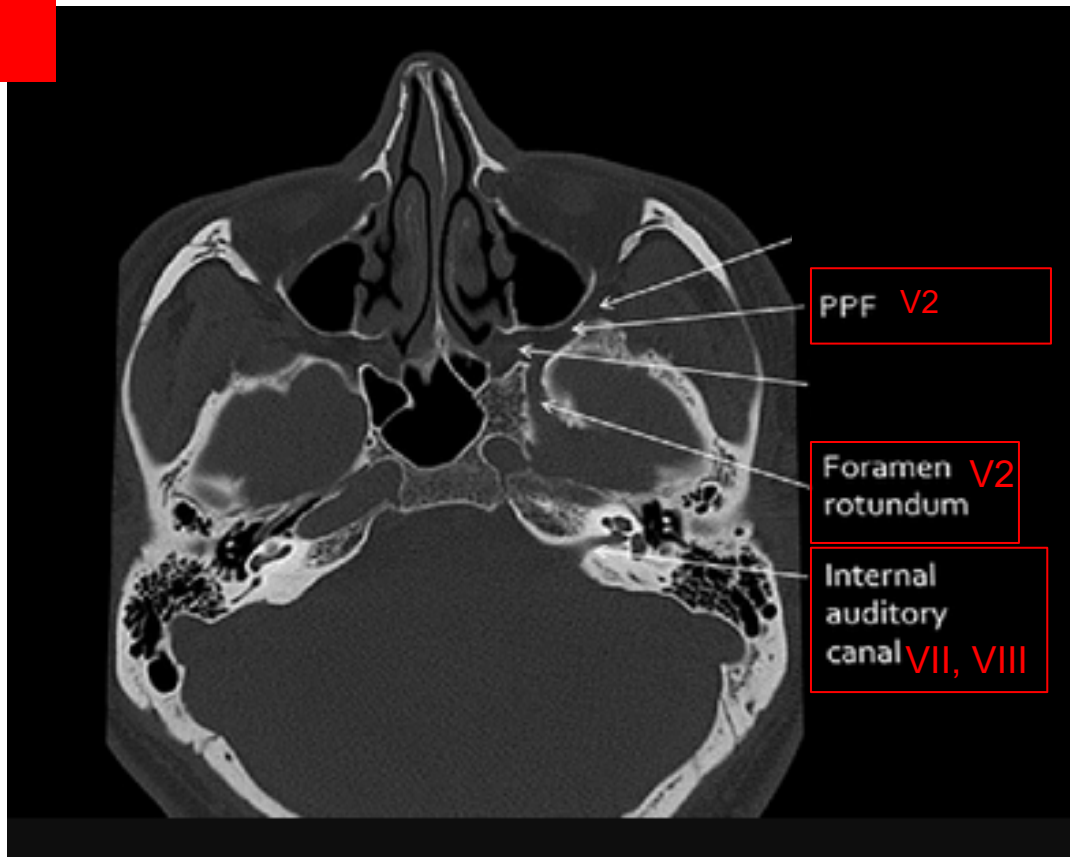

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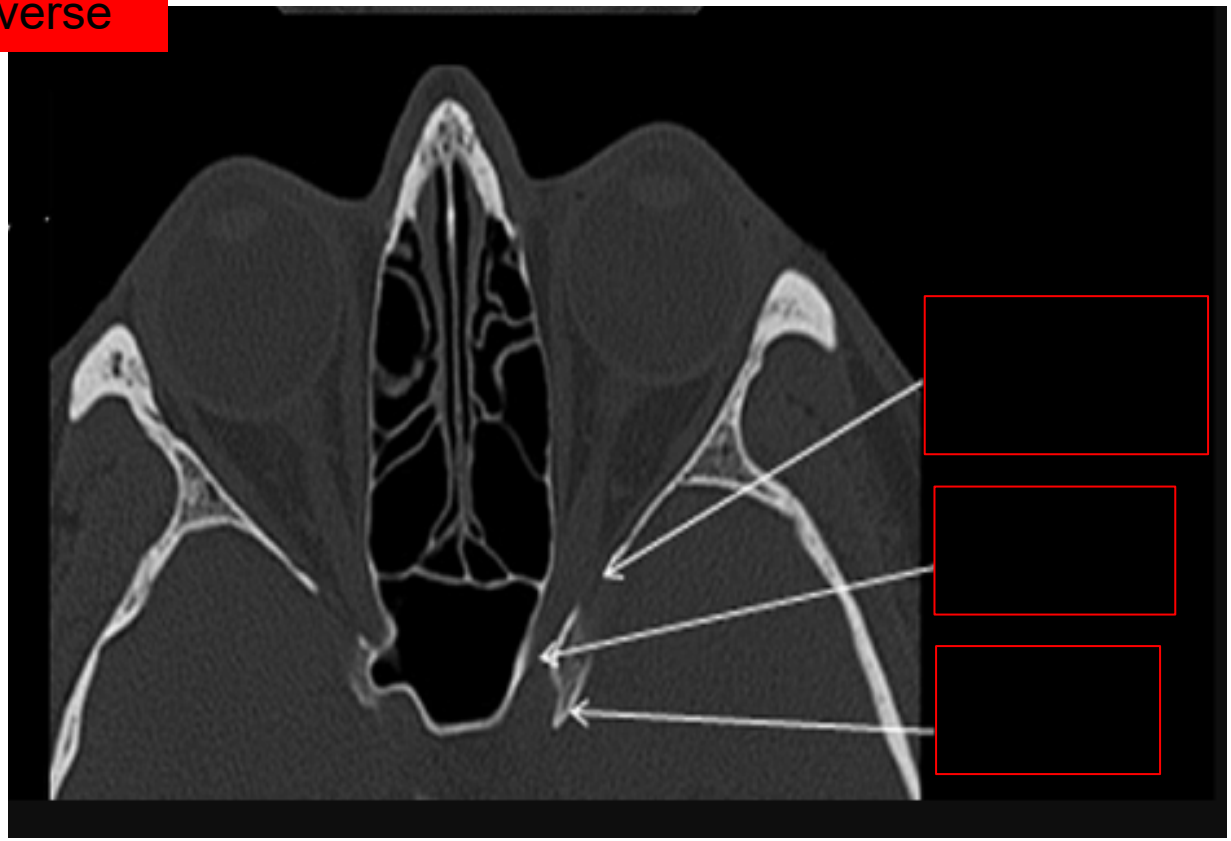

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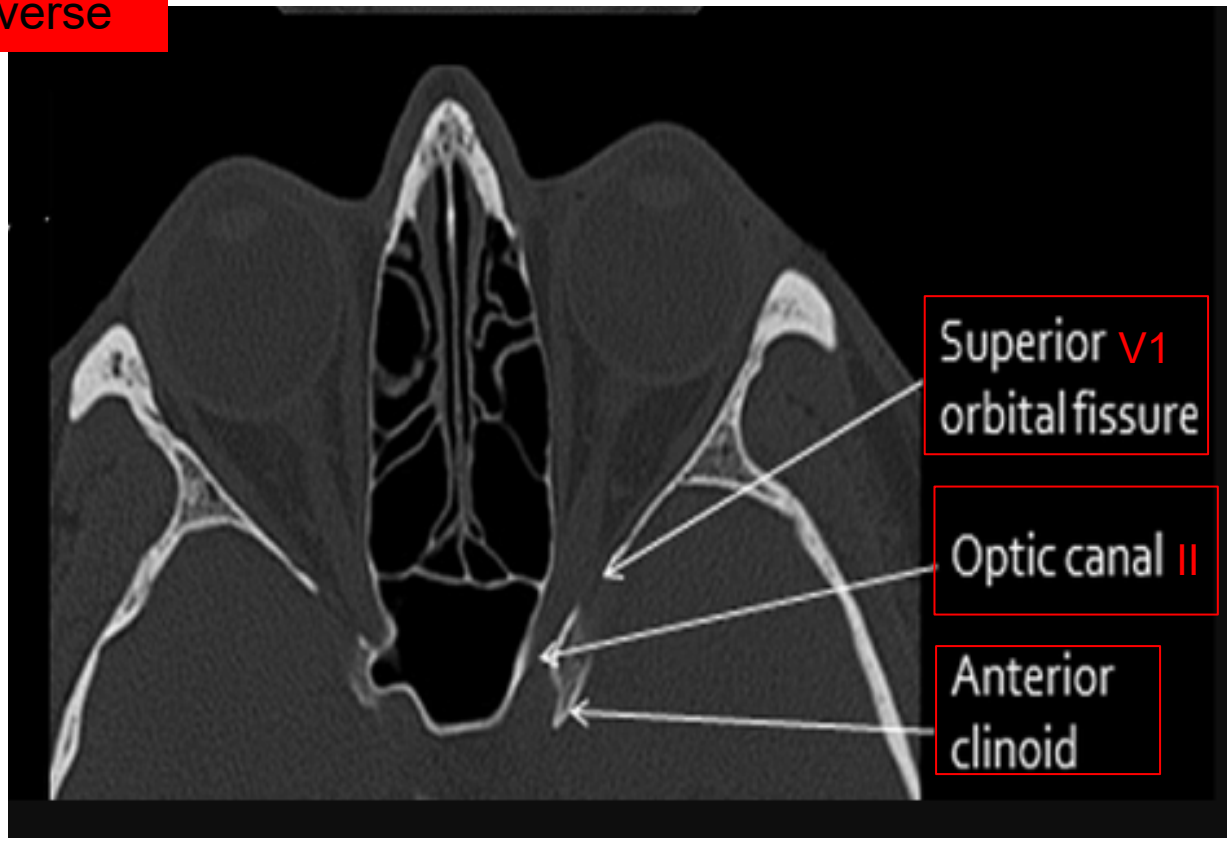

MRI Skull Base

What sequence is this?

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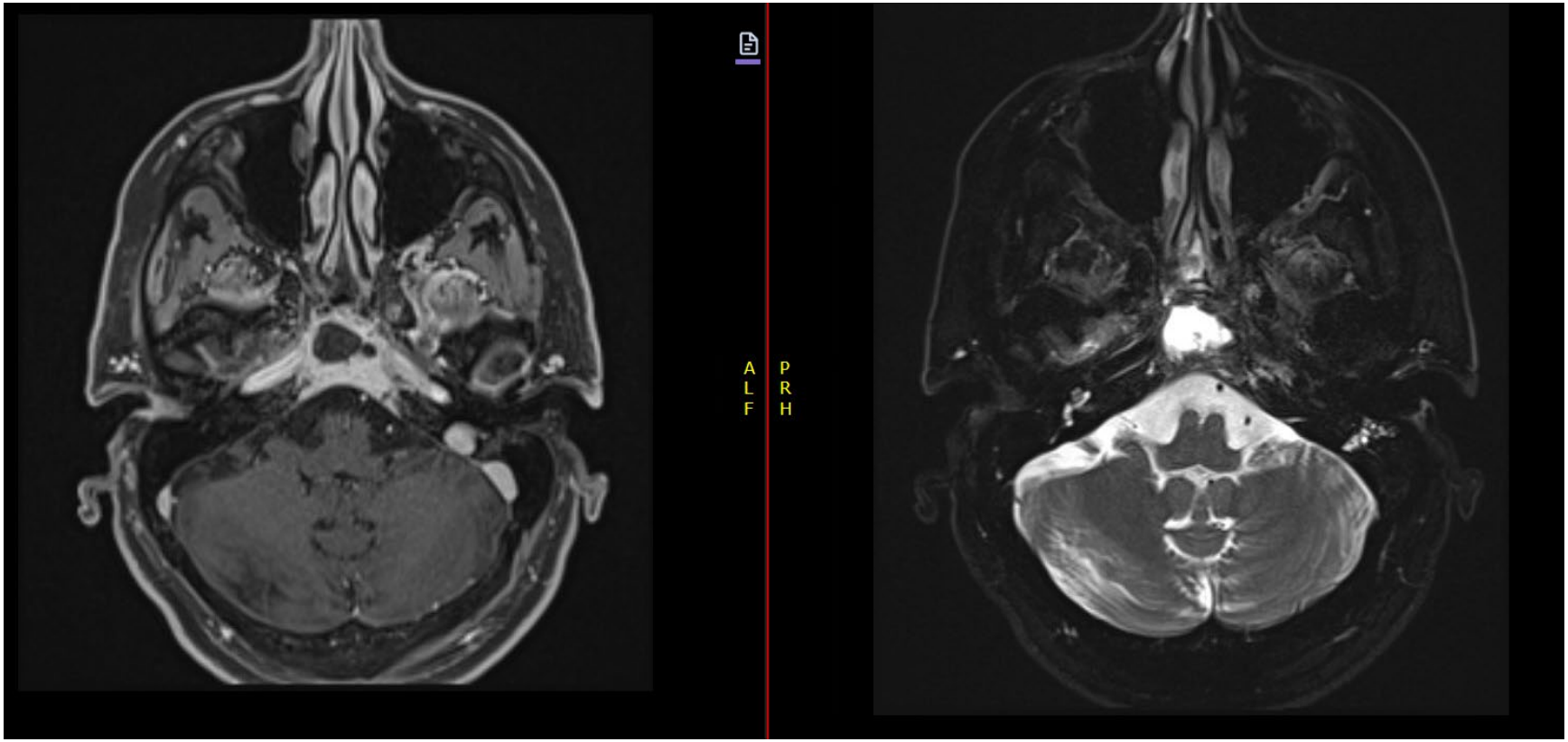
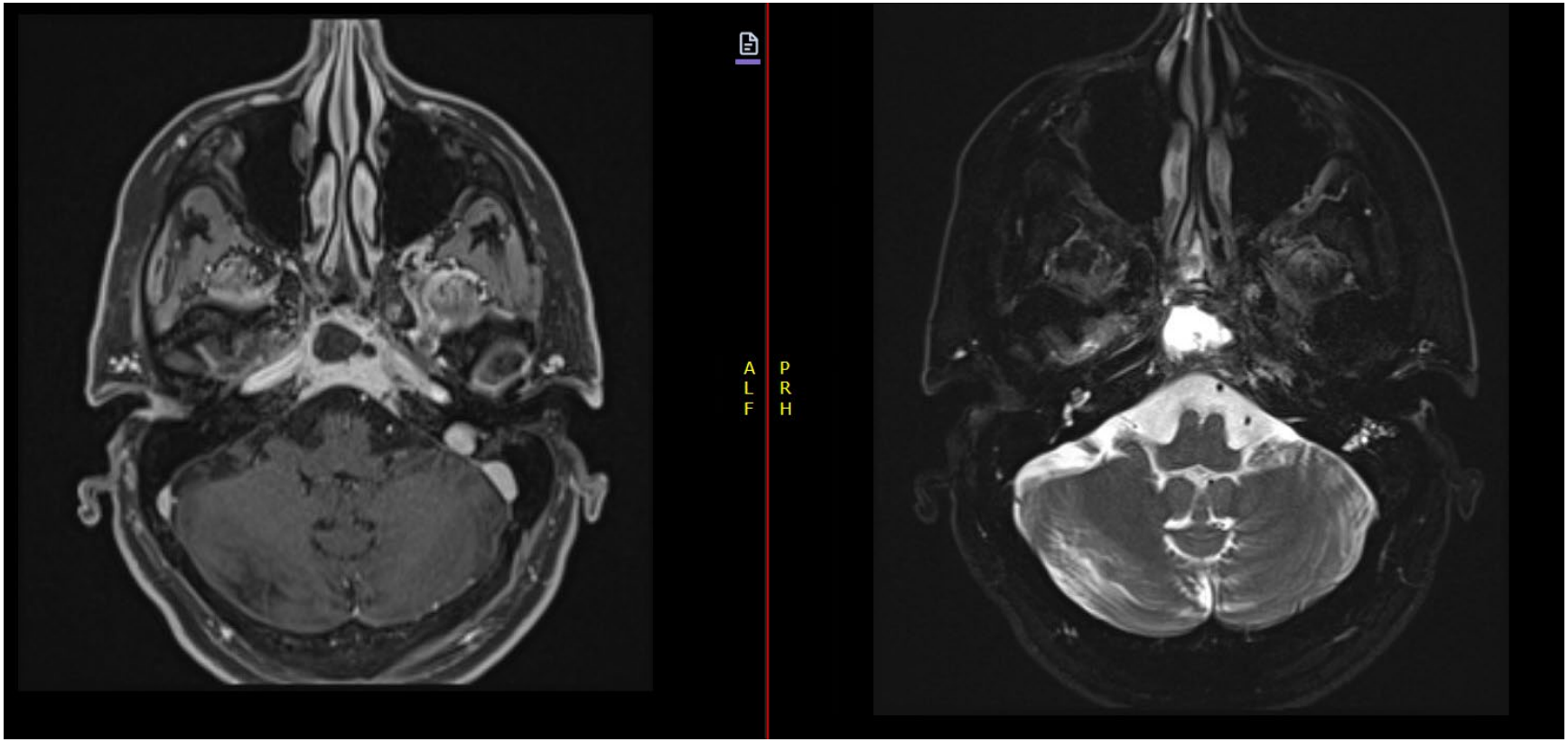


MRI Skull Base

T1 post contrast

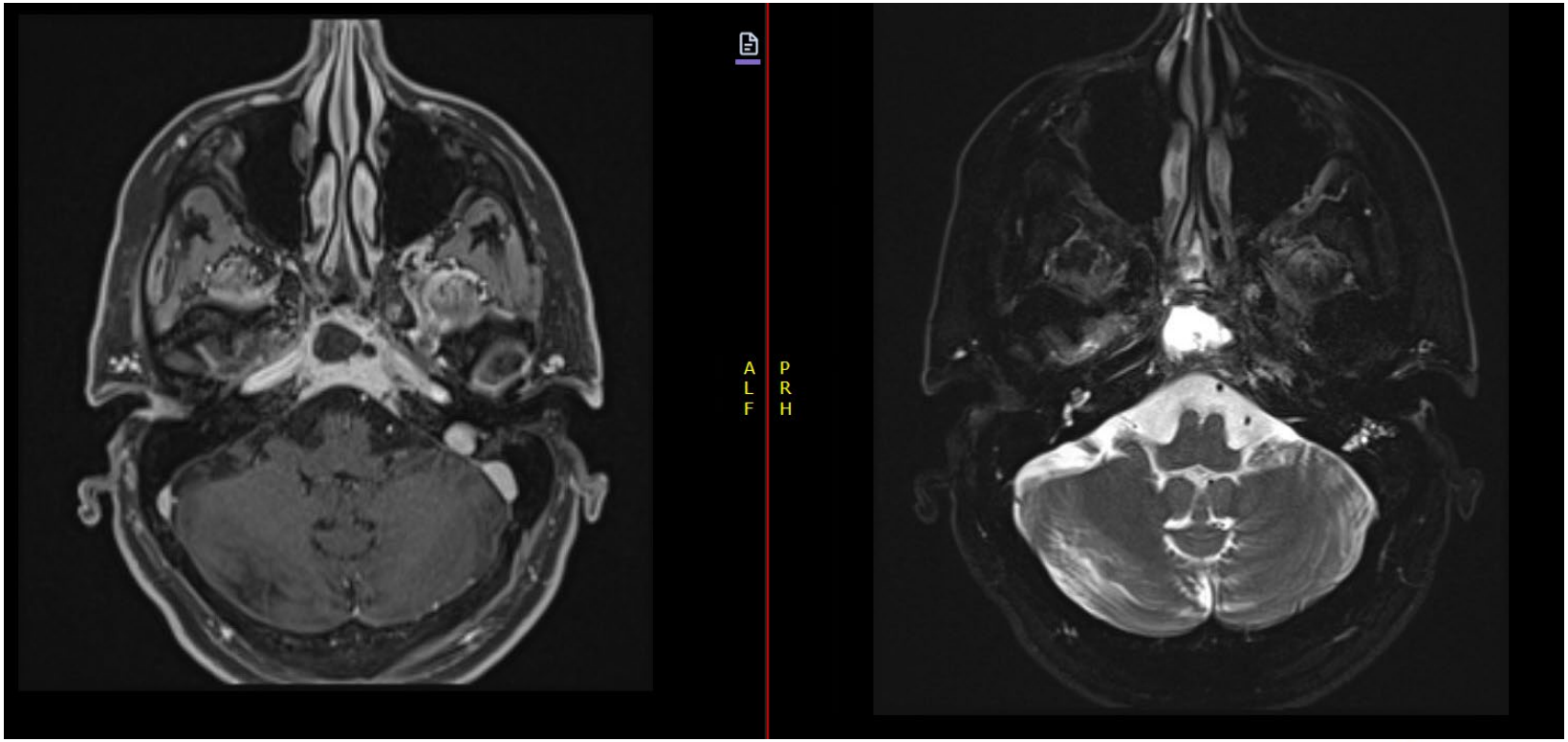
T2



Pro tip: T1 pre contrast can also be helpful when looking at bone invasion.

MRI Skull Base

Destructive lesion in posterior upper NPX, extensive involvement of **clivus**, T2 hypointense signal with diffusion restriction, contrast enhancement, cystic/necrotic changes. Laterally, the lesion **marginates the lacerum and proximal cavernous segments of the ICA as well as inferior petrosal sinuses.** Superior extension into dominant **left sphenoid sinus**. Inferiorly marginates the left hypoglossal canal without evidence of extension into the canal. No extension into the prepontine cistern.



Next step?

Needs a biopsy!

- Nasal endoscopy with biopsy
- Invasive non-keratinizing squamous cell carcinoma

What additional stains would you like to get on your pathology?

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- **EBV**- in situ hybridization for EBER (EBV-encoded small RNAs)
  - If positive, should obtain pre-treatment plasma EBV DNA levels
- If EBV negative, think of **HPV** immunohistochemistry- especially in non-endemic areas (United States and Northern Europe)
  - P16 IHC and HPV DNA/RNA ISH or HPV PCR

- This patient has invasive non-keratinizing squamous cell carcinoma, **HPV associated**

Pathology

TABLE 2: WHO Classification for Nasopharynx Cancer

WHO Classification	US Incidence	Endemic Incidence	Notes
Keratinizing	25%	2%	WHO type I (squamous cell carcinoma), associated with smoking and HPV
Non Keratinizing - *Differentiated*	12%	3%	WHO type II (transitional cell carcinoma)
Non Keratinizing - *Undifferentiated*	63%	95%	WHO type III (lymphoepithelial carcinoma), Endemic, associated with EBV, most favorable prognosis
Basaloid	-	<0.2%	Aggressive clinical course, poor survival

EBV and HPV Related NPX Cancer

- EBV related- very common in endemic regions (South-Eastern China)
- HPV related- more common in nonendemic, low incidence regions
- Extremely rare to be co-infected
- Non-virally related Risk Factors: salt cured food, salted fish, preserved or fermented foods, smoking, family history

- Remember: most studies on NPX are from China where the populations were largely EBV driven

Next step?

PET-CT

- Hypermetabolic 3.2 cm nasopharyngeal mass, associated hypermetabolic **bilateral** cervical lymphadenopathy
- Stable non-FDG avid 9 mm nodule in RUL

How would you stage this patient?

How would you stage this patient?

- cT3N2M0 Stage IVA

- T3 based on bone and sinus invasion
- N2 based on bilateral cervical LN seen on PET

TABLE 3: AJCC 8TH ED. (2017) STAGING FOR NASOPHARYNX CANCER

Tis	Carcinoma in situ	N1	Unilateral metastasis and/or unilateral or bilateral metastasis in RPNs, ≤6 cm, above caudal border of cricoid	Prognostic Stage Groups			
T0	No tumor identified, but EBV-positive cervical node involvement	N2	Bilateral metastasis, ≤6 cm, above caudal border of cricoid	I	T1	N0	M0
T1	Confined to nasopharynx or extends to oropharynx and/or nasal cavity without pharyngeal involvement	N3	Unilateral or bilateral metastasis in cervical lymph node(s), >6 cm in greatest dimension, and/or extension below caudal border of cricoid cartilage	II	T0-1 T2	N1 N0-1	M0
T2	Extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)			III	T0-T2 T3	N2 N0-N2	M0
T3	Infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses	M1	Distant metastasis	IVa	T4 Any T	N0-N2 N3	M0
				IVb	Any T	Any N	M1
T4	Intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond lateral surface of lateral pterygoid muscle						

How would you treat this patient?

Treatment Options for T2-T4 or N+ M0 NPX

- Induction CHT → ChemoRT (Sun et al PMID 27686945, Zhang et al PMID 35709465)
- ChemoRT → Adjuvant CHT (Al Sarraf et al PMID 9552031)
- ChemoRT (Chen et al PMID 22154591)

Referrals prior to starting RT

Referrals to consider prior to starting RT

- Dentistry
- Speech & Swallow
- Nutrition
- Audiogram

Induction paradigm

- Induction CHT Options:
  - TPF (cisplatin, fluorouracil, docetaxel q3 weeks x 3 cycles)
  - Gemcitabine/Cisplatin (q3 weeks x 3 cycles)
  - Cisplatin/5FU (q3 weeks x 2-3 cycles)
- Restaging scans to assess response
- Start chemoradiation 3-8 weeks after start of the third cycle of induction chemotherapy

How would you simulate this patient, what is radiation dose, and what do your treatment volumes contain

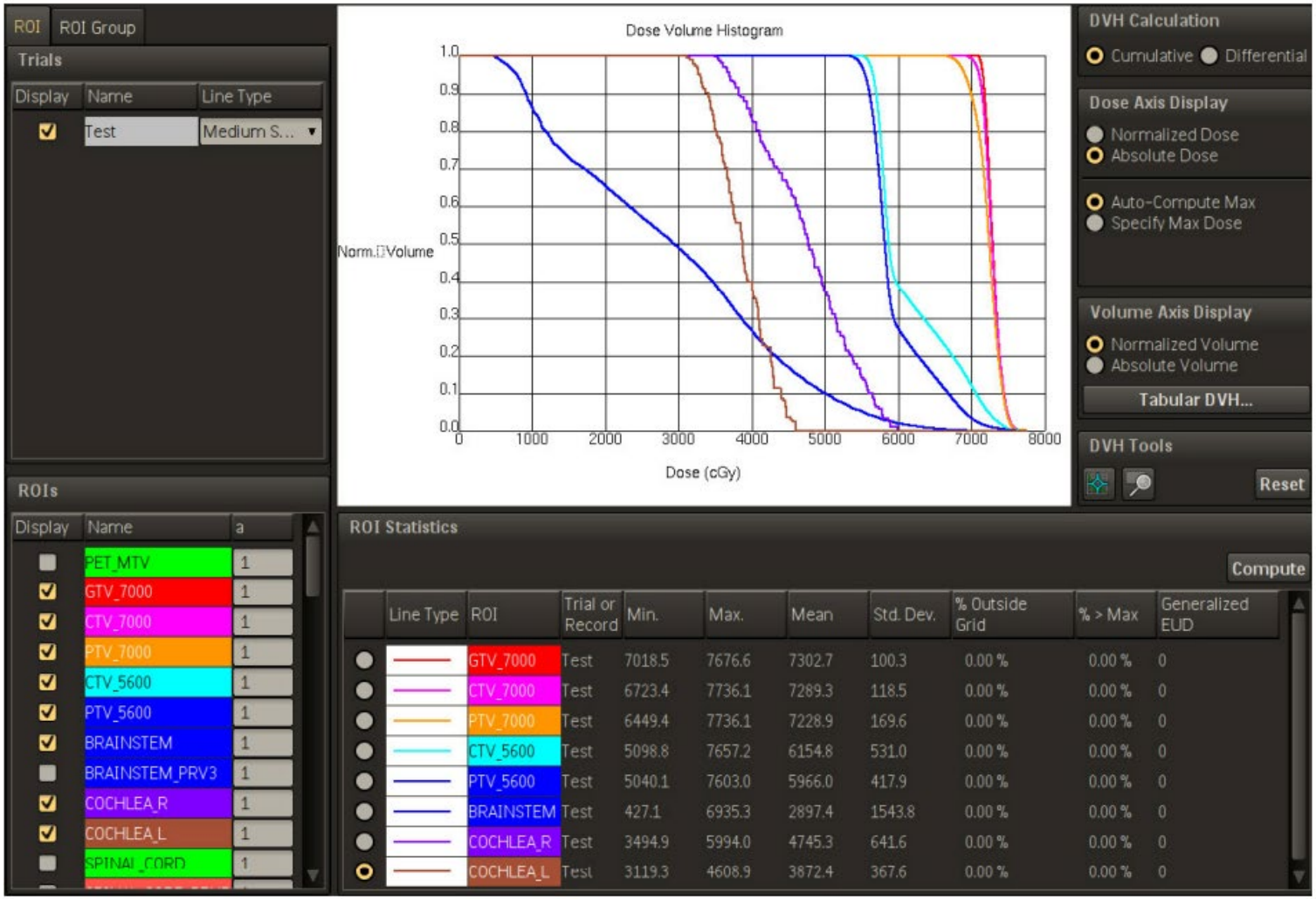
Radiation Paradigm

- Supine, arms at side, IV contrast, 5 pt mask, mouthpiece
  - Mouthpiece used to move tongue away from the soft palate
- Concurrent chemoRT
  - Cisplatin
    - Bolus- 100 mg/m^2 weeks 1, 4, and 7
    - Weekly- 40 mg/m^2 weekly

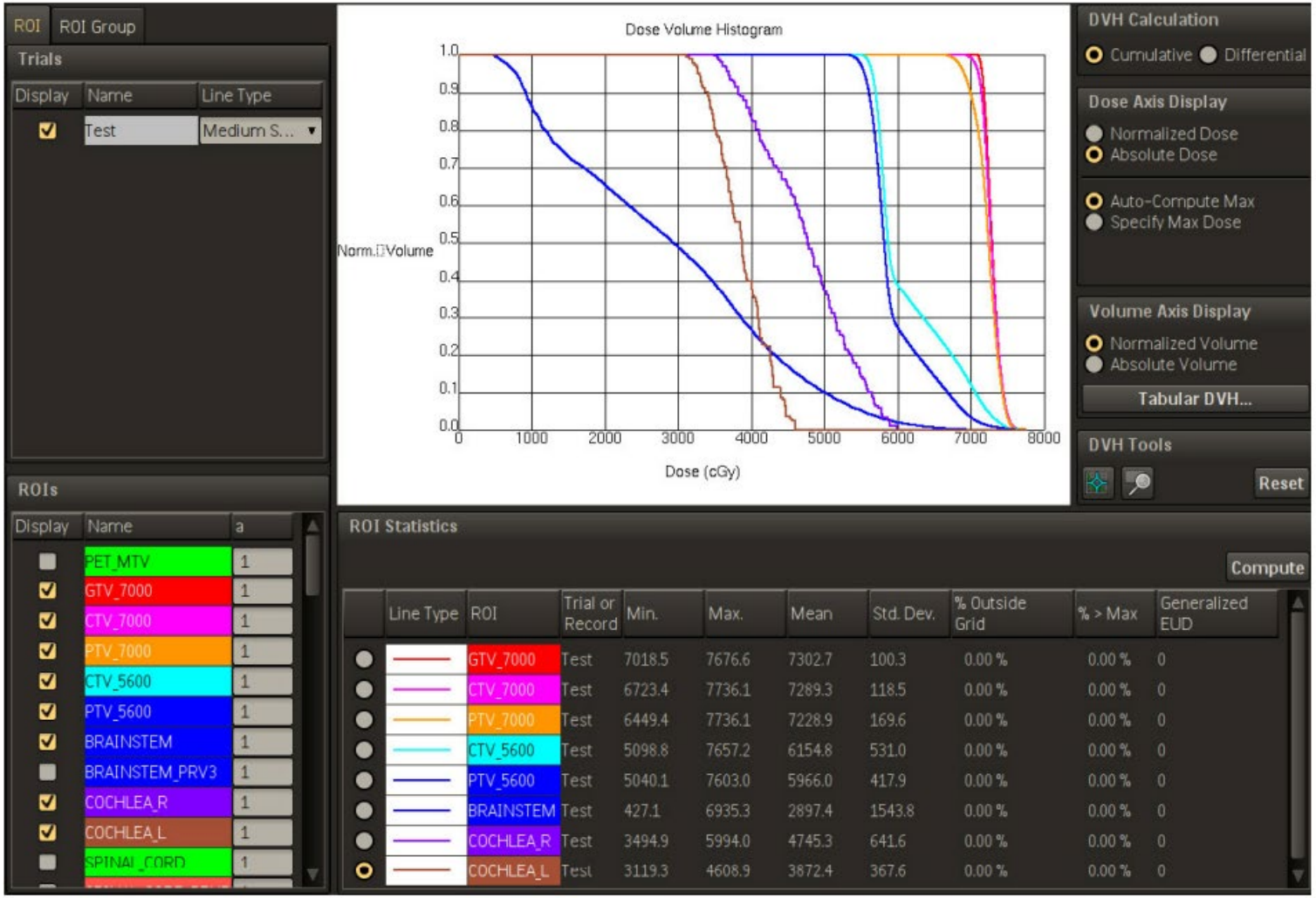
Radiation Paradigm

- RT:
  - GTV: 70 Gy in 35 fx to gross disease
  - CTV (elective nodal) 56 Gy to **bilateral RPNs, level II-V**; treat 1B in node positive patients or those with primary tumor extending to nasal cavity, hard palate, or maxillary sinus
  - CTV (elective volume) (56-63Gy): entire NPX, anterior 1/3 clivus (entire if clivus involved), foramen ovale, foramen rotundum, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus (entire sphenoid sinus if T3-T4), cavernous sinus (if T3-T4), posterior fourth of the nasal cavity and maxillary sinuses

Would you accept this plan?



Would you accept this plan?- No!



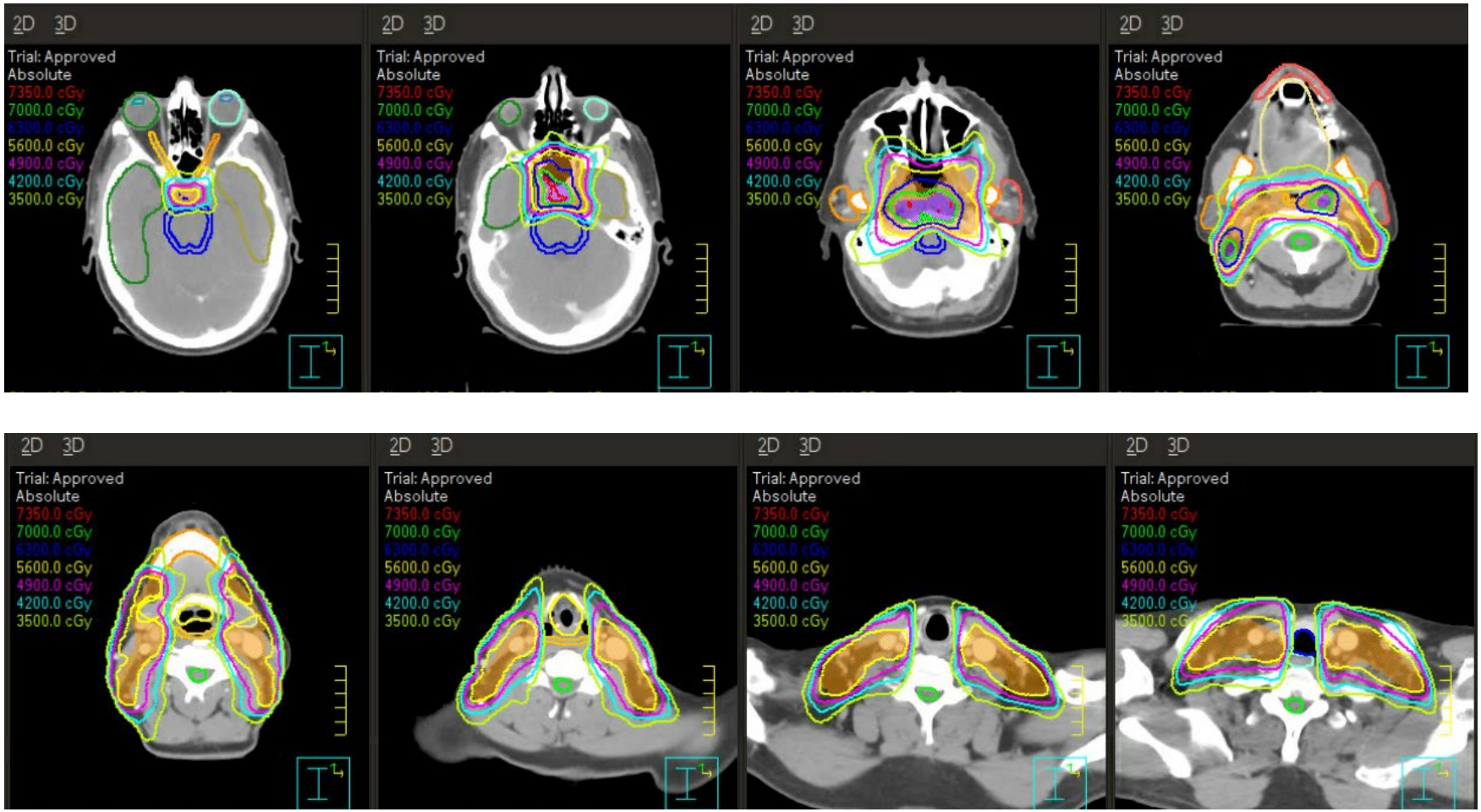
Attempt to increase PTV coverage to >95%

Brainstem dose is too high!

Important constraints to remember

- Brainstem 54 Gy max dose to 0.03 cc
  - Must compromise tumor coverage for OAR constraints, can reduce PTV to 0mm posteriorly
  - Acceptable variation up to 60 Gy
- Spinal cord 45 Gy max dose
  - Acceptable variation up to 60 Gy
- Optic nerves/chiasm 54 Gy max dose
  - Acceptable variation up to 56 Gy
- Mandible 70 Gy max dose
  - Acceptable variation up to 75 Gy
- Brachial Plexus 66 Gy max dose
  - Acceptable variation up to 70 Gy
- Temporal lobe 70 Gy max dose
  - Acceptable variation up to 72 Gy

Example of acceptable NPX plan



What are possible side effects?

- Xerostomia, dysphagia, otitis media, hearing loss, trismus, soft tissue or bone necrosis, brain necrosis (temporal lobe resulting in memory loss, seizures), CN dysfunction, hypothalamic-pituitary and/or thyroid dysfunction, secondary tumors, carotid stenosis, carotid bleed

Follow Up

- H&P
  - Year 1 every 1-3 mo
  - Year 2 every 2-6 mo
  - Year 3-5, every 4-8 mo
  - >5 years, every 12 mo
- Scans
  - PET at 3-6 mo to assess treatment response
  - MRI skull base and CT neck/chest q3-6 months for first two years
- Check TSH yearly
- Consider monitoring EBV-DNA or HPV-DNA
- Most common site of failure: distant
- Majority of failures occur in the first 2 years

Important Studies

Evidence for Adjuvant Chemo

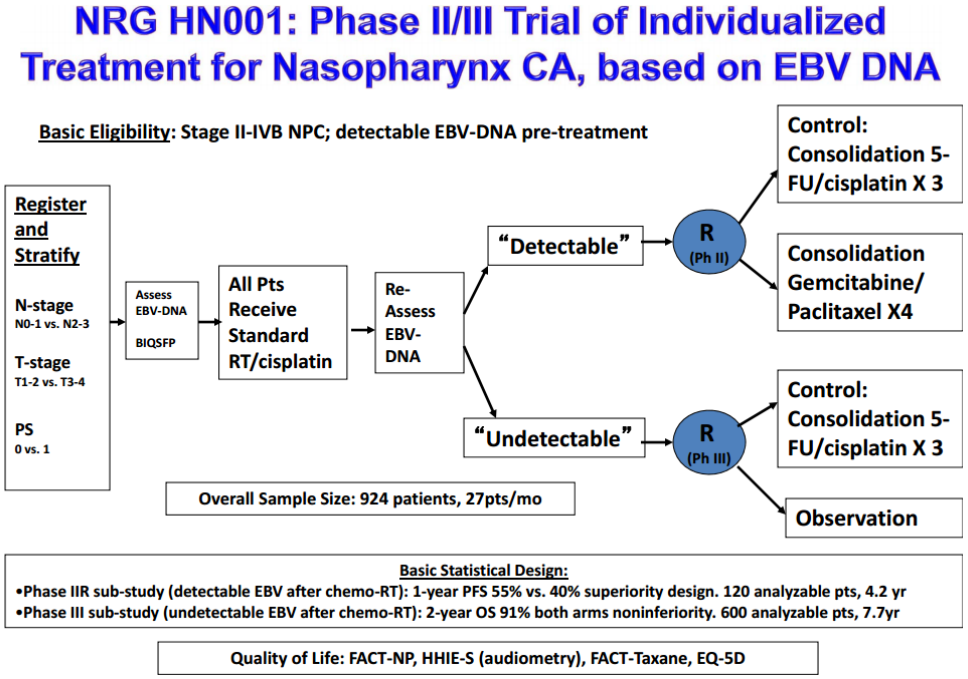
	Al-Sarraf, Intergroup 0099 **(JCO 1998, PMID 9552031)**	**Chen, Sun Yat-sen China** **(Lancet Onc 2012, PMID 22154591)**
Inclusion criteria	193 pts with biopsy proven stage III-IV (M0) NPX cancer. Note that AJCC 4th edition included N1 pts in stage III (now stage II).	508 pts with stage III/IV (T3-4N0 excluded)
Randomization	RT alone vs RT with concurrent bolus cisplatin and adjuvant CHT with cisplatin and 5-FU	Concurrent chemoRT +/- adjuvant CHT (cisplatin 80 mg/m2 and 5-FU 800 mg/m2 for 120 hours q4weeks x3 cycles).
Primary Endpoint	PFS and OS	Failure free survival (FFS)
Outcomes	3 yr PFS rate was 24% for RT vs 69% for CRT arm. 3 yr survival rate was 47% for RT vs 78% for CRT	2-yr FFS rate was 84% in concurrent only arm and 86% in concurrent + adjuvant arm (p=0.13)
Conclusion	**Concurrent and adjuvant CHT with RT improves OS and PFS** for Stage III-IV nasopharyngeal cancer	**Adjuvant CHT did not improve FFS**
Notes	Unable to conclude whether the concurrent and/or adjuvant chemo resulted in the survival benefit.	Did not use non-inferiority design, 18% randomized to adjuvant CHT didn't receive it, nearly 60% didn't complete concurrent chemo, 50% required RT dose reduction, and 70% had treatment delays.

Evidence for Induction Chemo

	Sun, China **(Lancet Onc 2016, PMID 27686945)**	**Zhang, China** **(JCO 2022, PMID 35709465)**
Inclusion criteria	480 pts, with Stage III-IVB (except T3-4N0)	480 patients with Stage III-IVB (excluding T3-4N0)
Randomization	Induction CHT (TPF: cisplatin, fluorouracil, docetaxel Q3 weeks x3 cycles) followed by chemoRT vs chemoRT alone	Induction CHT (Gemcitabine/Cisplatin q3 weeks x3 cycles) followed by chemoRT vs chemoRT alone
Primary Endpoint	FFS	FFS
Outcomes	3-year FFS increased from 72% to 80% (p=0.034) in favor of induction chemo and improved 3 yr OS (92% vs 86%, HR 0.59, 95% CI 0.36-0.95)	Induction arm had a significantly higher 5-year OS (87.9% v 78.8%, P = .001), improved FFS (81% vs 67% p<0.001), improved DMFS (90% versus 78% p<0.001) and a comparable risk of late toxicities (≥ grade 3, 11.3% v 11.4%).
Conclusion	**Induction CHT significantly improved 3-yr FFS** compared to chemoRT alone.	**Induction CHT with cis/gem significantly improved FFS and OS over chemoRT alone**
Notes	Induction CHT was associated with increased grade 3/4 toxicity: 42% vs 17% neutropenia, 41% vs 17% leukopenia, 41% vs 35% stomatitis.	No adjuvant CHT was used

Role of EBV

- EBV is primary etiologic agent in pathogenesis of nasopharynx carcinoma, and EBV levels both pre and post treatment can be used as prognostic factor for survival.
- Patients with pre-treatment ranging from <1,500 copies/mL to <4,000 copies/mL tend to have improved survival.
- Multiple studies have shown that detectable EBV after definitive RT may serve as poor prognostic marker, correlating to locoregional failure, distant metastasis, and death. (PMID: 15190138, 17135642)
- NRG HN001 is an ongoing phase II/III study of individualized treatment for NPC based on post-treatment EBV DNA.



Metastatic Nasopharynx

- **You, China (JAMA Oncol 2020, PMID 32701129):**
  - Randomized trial of 126 patients with de novo metastatic NPX cancer who had at least a partial response to 3 cycles of cisplatin and 5-FU
  - Randomized to further chemotherapy +/- sequential radiotherapy to 70 Gy
  - Primary Endpoint: OS
  - Median follow up (MFU) 26.7 mo, RT improved 2 year OS (76.4% vs 54.5%, p=0.004), increased grade 3+ mucositis.
  - Conclusion: locoregional RT results in improved OS for de novo metastatic NPC patients who have response to chemotherapy

Recurrent Nasopharynx

- **You, China (Lancet 2023, PMID 36842439):**
  - Phase III prospective randomized trial at 3 Chinese hospitals of 144 patients with recurrent, locally advanced nasopharyngeal cancer previously treated with RT
  - Randomized to standard fractionation 54 Gy/27 fx vs hyperfractionation 65 Gy/54 fx BID
  - Primary Endpoints: 3 yr OS and incidence of late grade 3-5 complications
  - MFU 45.0 mo, Hyperfractionated arm with superior 3 yr OS (74.6% vs 55.0%, HR 0.54, p=0.014) and fewer grade 3-5 RT induced toxicities (34% vs 57% p=0.023). Fewer grade 5 late complications in hyperfractionated cohort (7% vs 24%)
  - Conclusion: Hyperfractionated RT for locally advanced recurrent NPX cancer results in superior OS with fewer late grade 3-5 toxicities

References

- Essentials of Clinical Radiation Oncology
- Uptodate
- NCCN Clinical Practice Guidelines- Head and Neck Cancers

Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com