Head and Neck Cancers with Perineural Invasion

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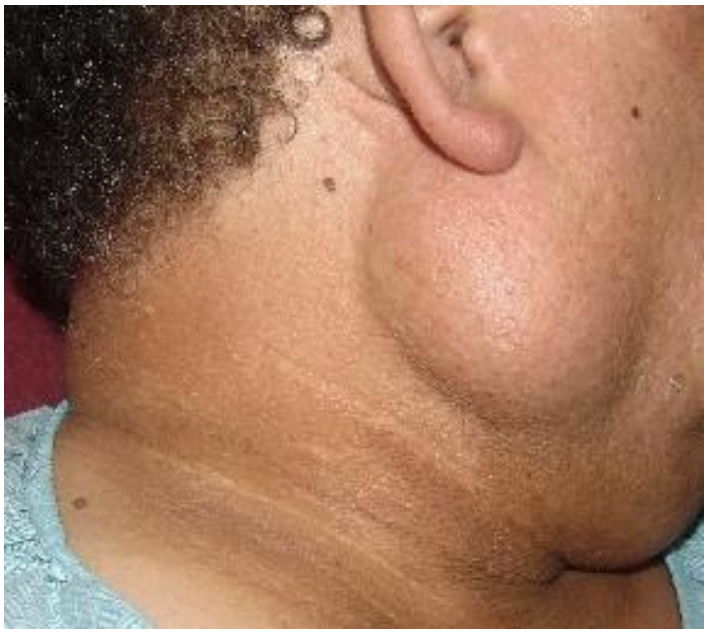
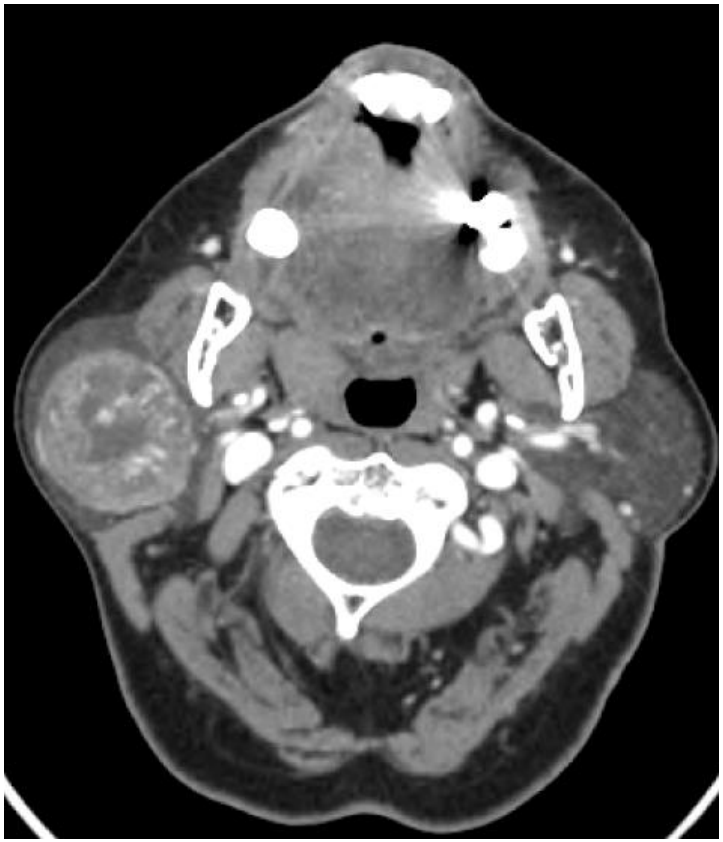
CASE I: PRESENTATION

- 68 Year old with slowly progressive painless mass in the right postauricular region
- Symptoms of neuropathic pain without facial nerve palsy
- Did not have advanced can cause dysphagia, sore throat, referred earache, trismus, numbness, and headache



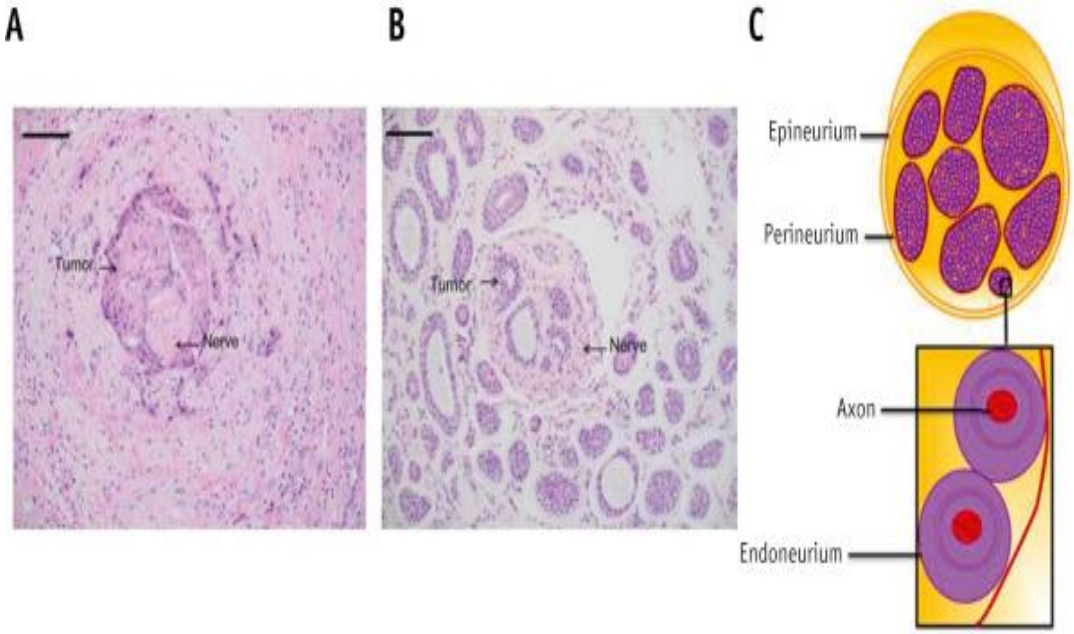
CASE I: WORKUP

- PET CT Showed a 4.3 cm mass with central lucency growing posterolaterally into the region of the soft tissues inferior and posterior to the right EAC
- MRI showed infiltrating tumor in the right parotid gland with extension to the inferior aspect of the right ear within the deep lobe of the right parotid gland. There is a cystic component noted suggestive of necrosis
- Biopsy showing fragments of invasive adenoid cystic carcinoma
- Right partial auriculectomy and parotidectomy showed adenoid cystic carcinoma
- Extensive perineural invasion (PNI) infiltration of the proximal facial nerve
- Stage IVA (pT4aN0M0) and referred for adjuvant radiation



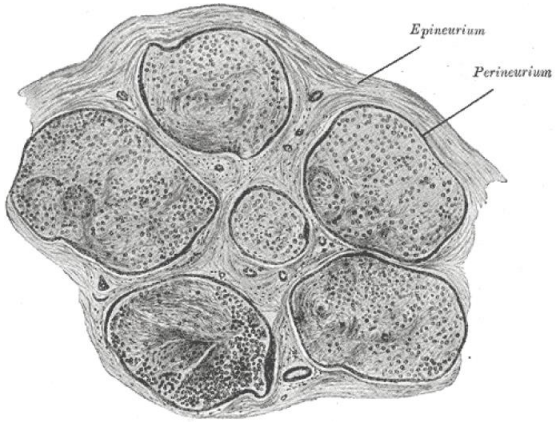
Perineural Invasion

- Tumor invasion of the nerves
  - 3 layers
    - Epineurium
    - Perineurium
    - Endoneurium
  - Categorization
    - Gross
    - Microscopic



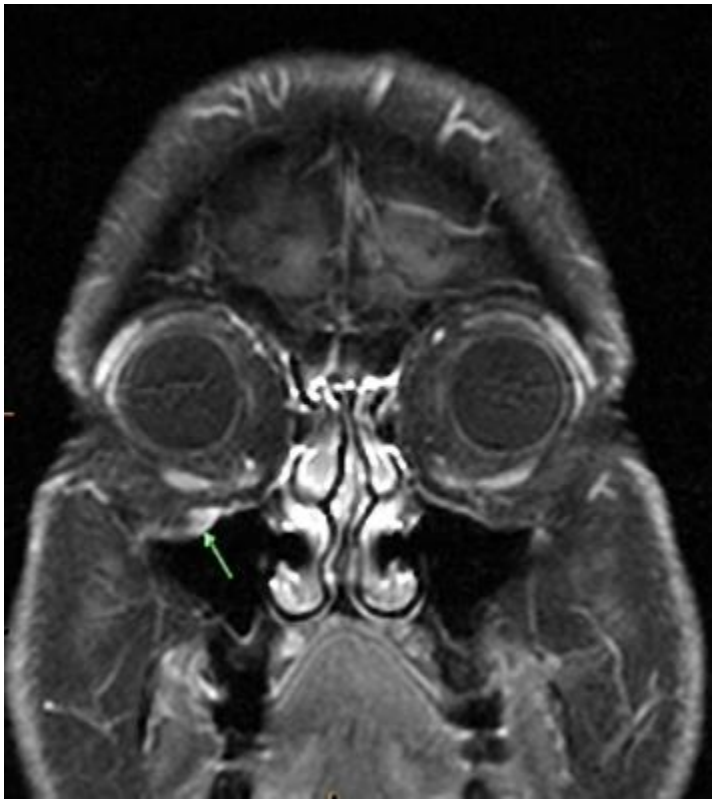
Perineural Invasion

- Histologies with high predilection
  - Nasopharyngeal Cancer
  - Paranasal Sinus/Nasal Cavity
  - Soft Tissue Sarcomas
  - Skin Cancers
    - Squamous cell carcinoma
  - Salivary Gland Carcinoma
  - Adenoid cystic
    - Highest association with PNI
    - 1-3 % of head and neck cancer
  - Mucoepidermoid
    - High association with PNI
  - Oral Cavity Cancers
    - Squamous cell carcinoma
    - Large number of cases with perineural spread
  - Melanoma
    - Desmoplastic variant
    - High rate of intracranial extension



Perineural Invasion

- In head and neck cancers tendency to spread along major nerves
- Retrograde conduit for intracranial extension
- Clinically asymptomatic until progression of pain, paresthesia, weakness of mastication can occur
- Predictor for skull base recurrence



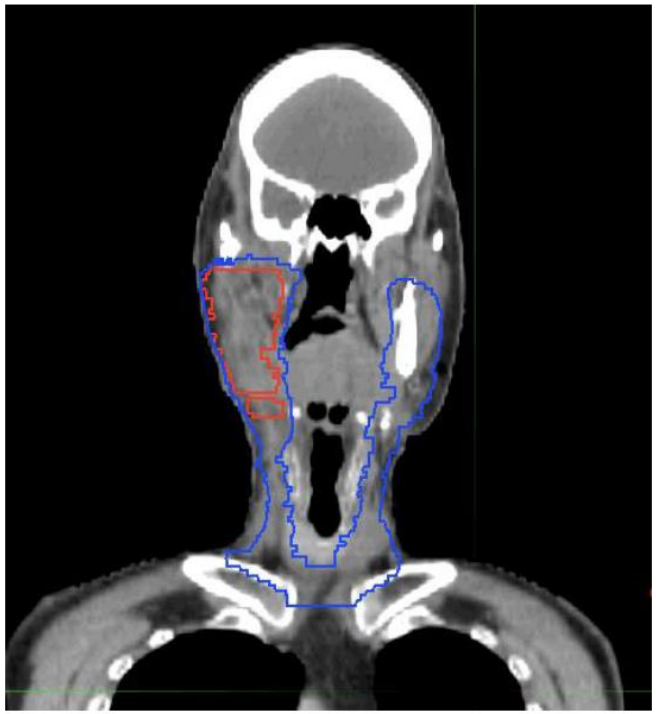
LRR increased with PNI

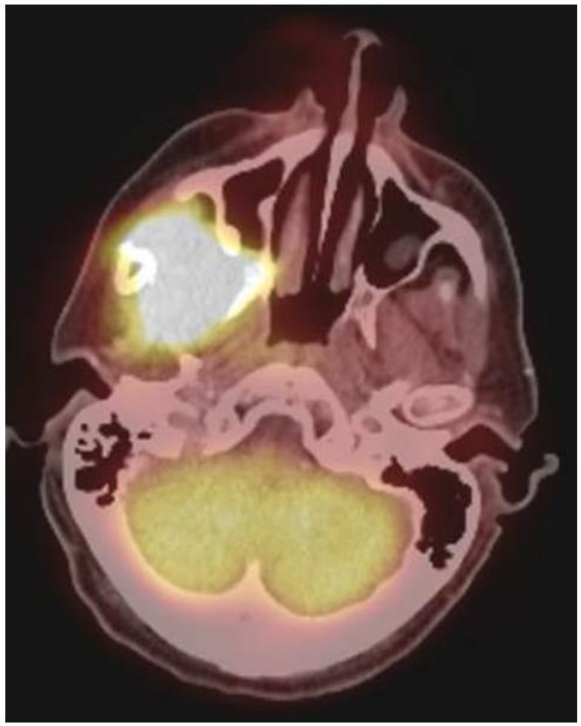
- Multiple reviews showing increase LRR with PNI compared to tumors without PNI

Authors	N	Sites	LRR (PNI+)	LRR (PNI-)
Tai et al (2011)	190	Oral tongue	22	8
Hinerman et al (2011)	226	Oral cavity	38	12
Gonzalez et al (2009)	522	Oral cavity	15	10
Langendijk et al (2005)	801	Mixed	31	22
Fagan et al (1998)	142	Mixed	23	9

PNI with high risk of Base of skull Recurrence

Infra-temporal fossa recurrence

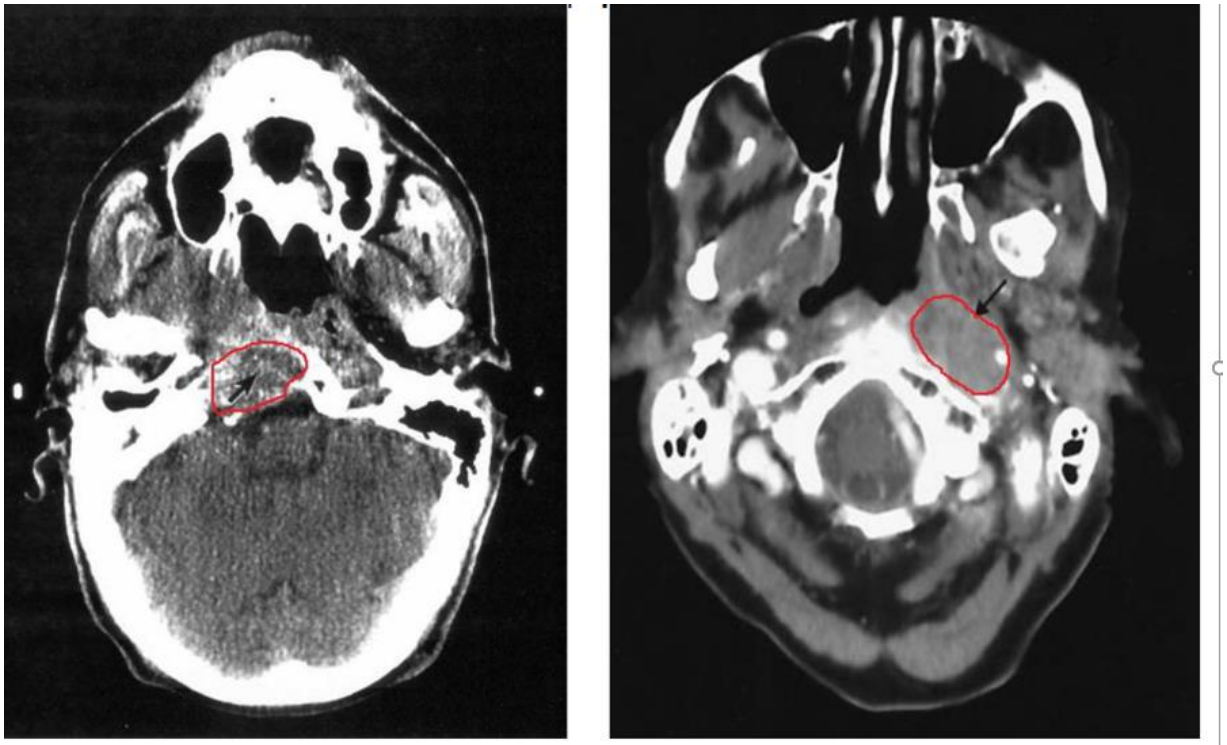




Chen et al, IJROBP 2011

PNI with high risk of Base of of skull Recurrence

- Ipsilateral High Cervical Neck



Eisbruch et al, IJROBP 2004

RT reduces rate of Base of Skull Recurrence in tumors with PNI

Base of skull recurrences after treatment of salivary gland cancer with perineural invasion reduced by postoperative radiotherapy

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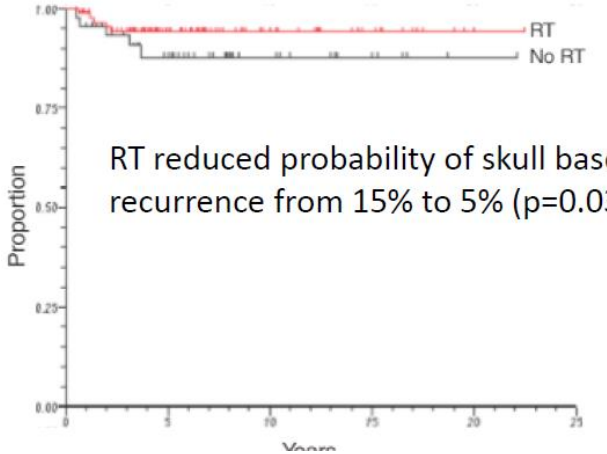
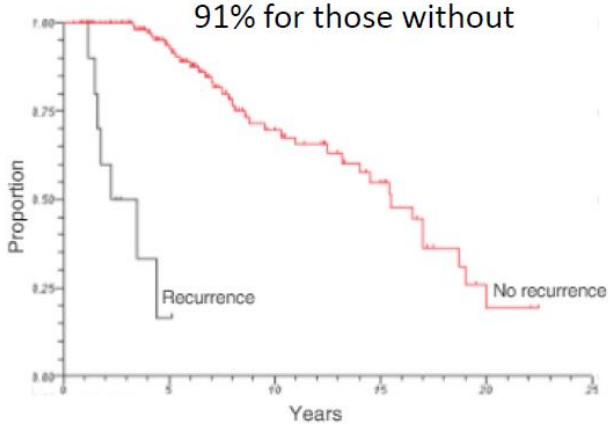
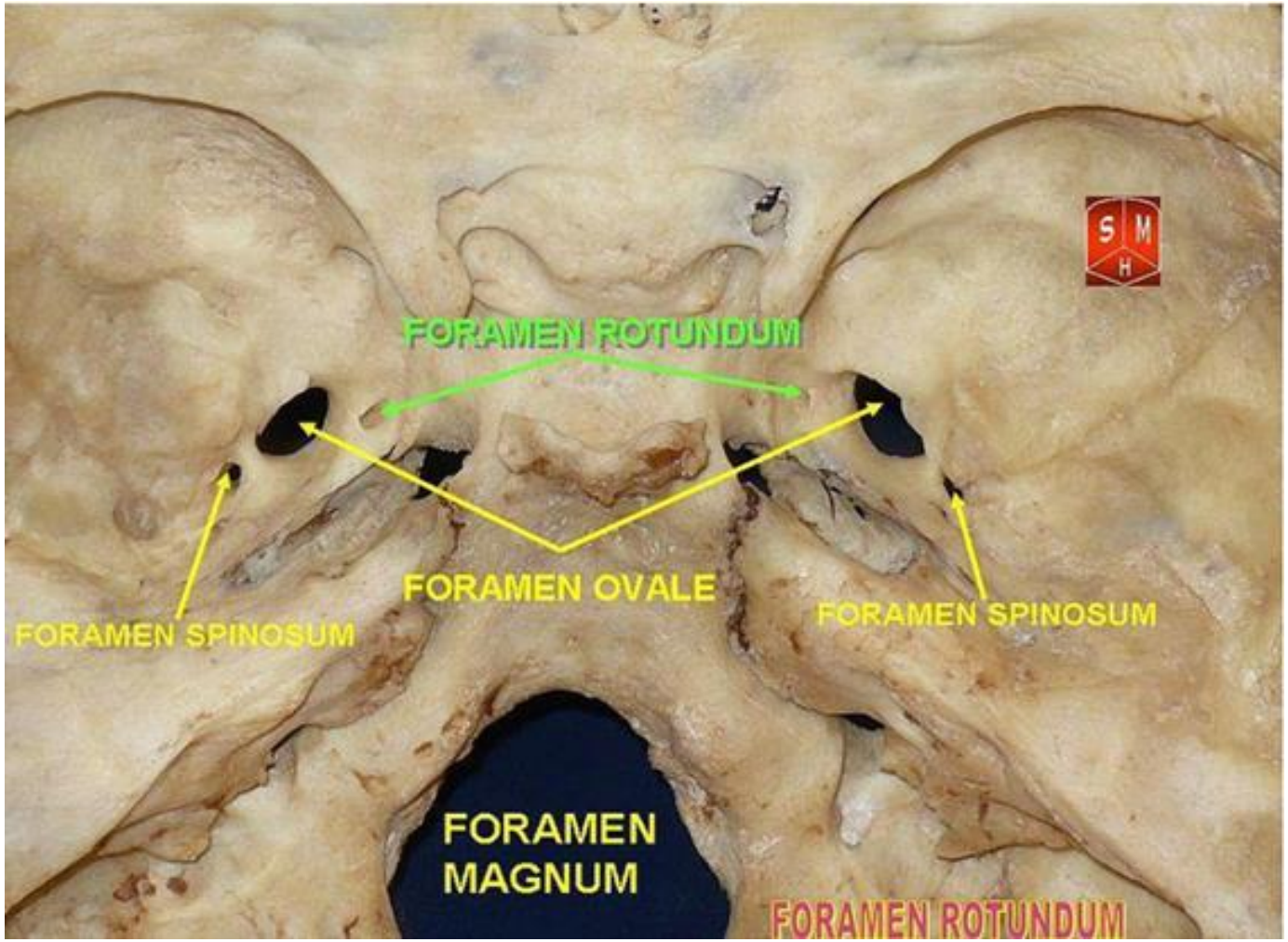


RT reduced probability of skull base recurrence from 15% to 5% (p=0.03)

Patients with skull base recurrence had 5-year OS of 9% compared to 91% for those without

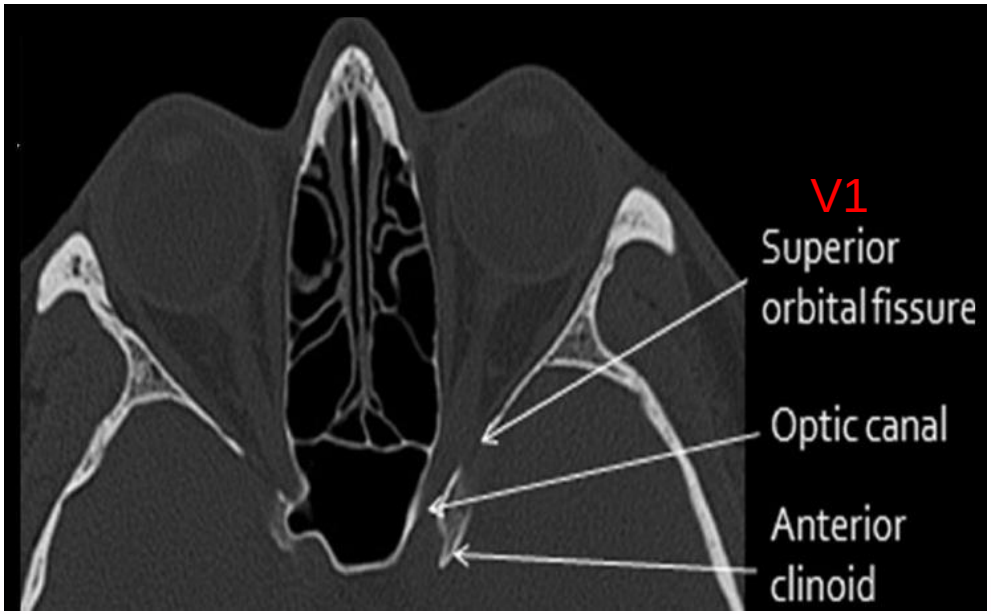


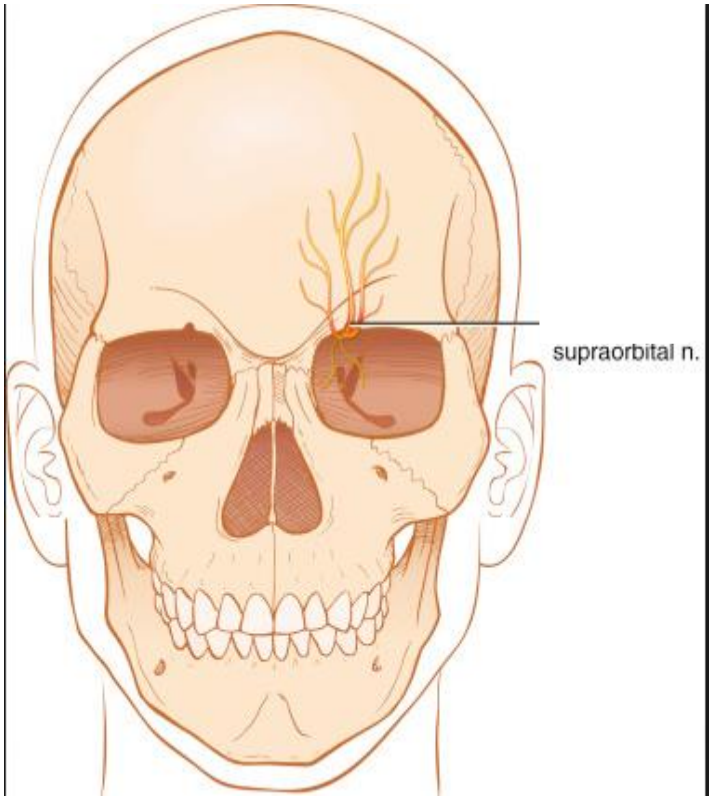
At Risk Base of Skull Foramina



Location of Tumor and PNI

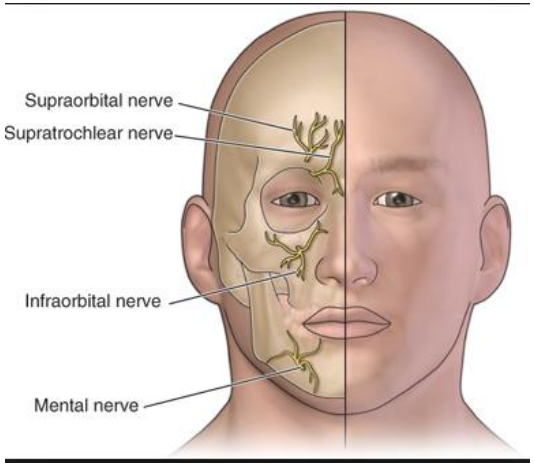
- Forehead
  - Supraorbital Nerve→V1→Superior orbital Fissure

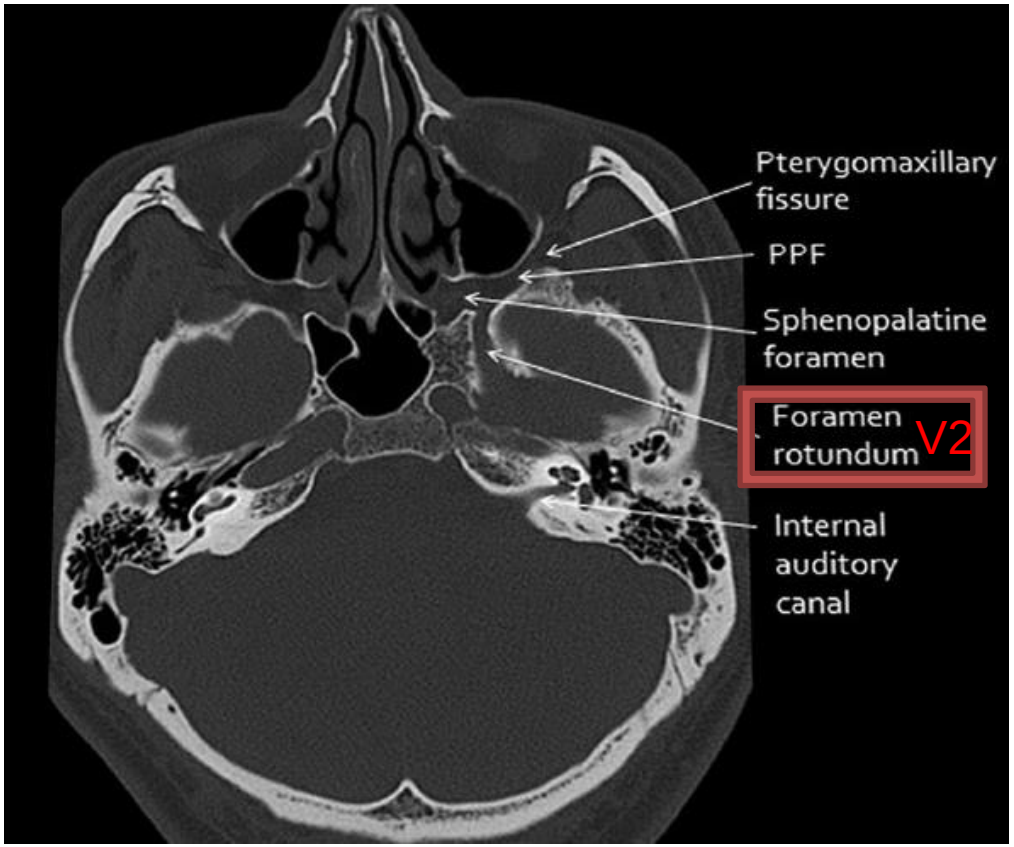




Location of Tumor and PNI

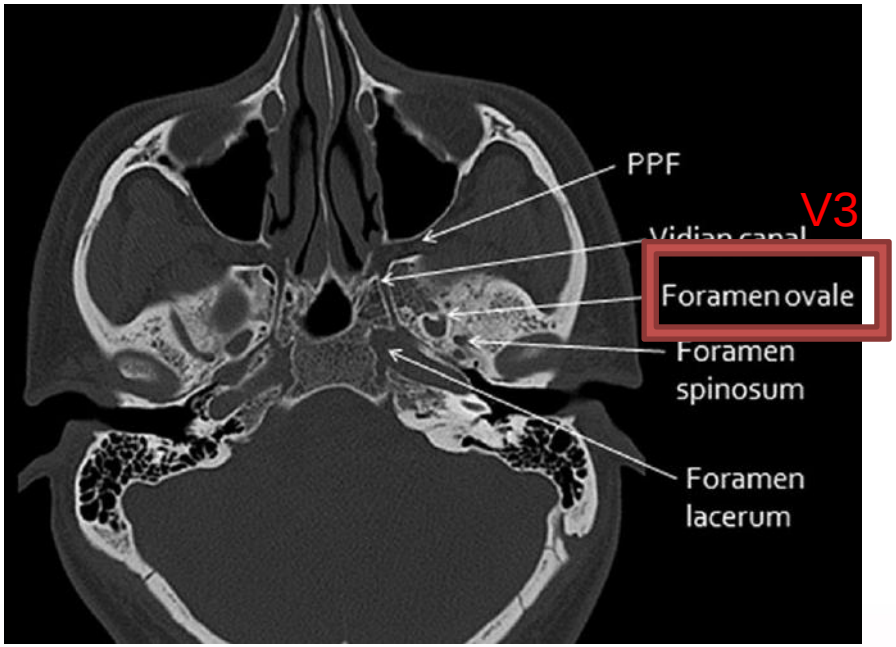
- Cheek
  - Infra-orbital nerve→ V2→Foramen Rotundum

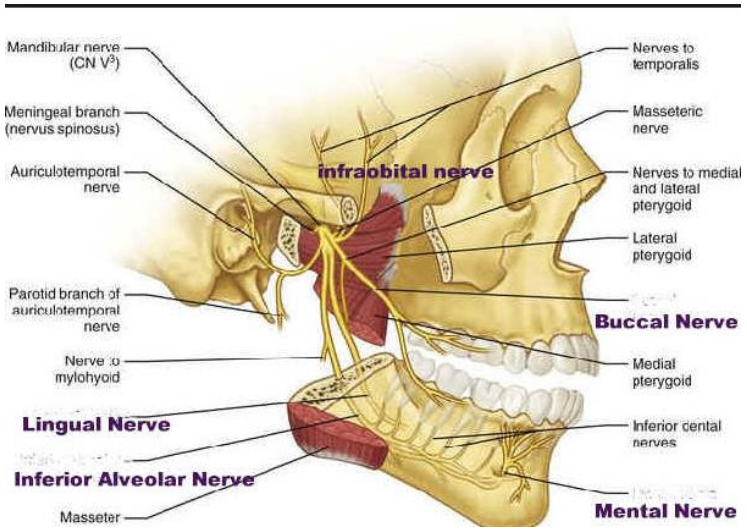




Location of Tumor and PNI

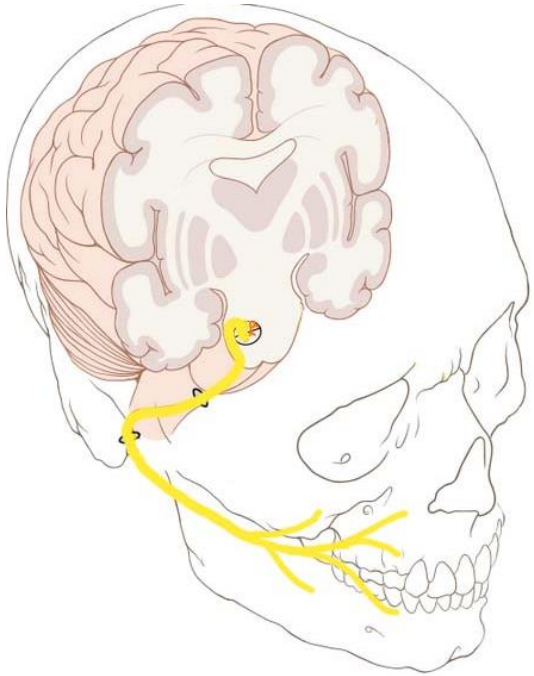
- Oral Cavity
  - Inferior alveolar nerve/lingual nerve→V3→Foramen Ovale

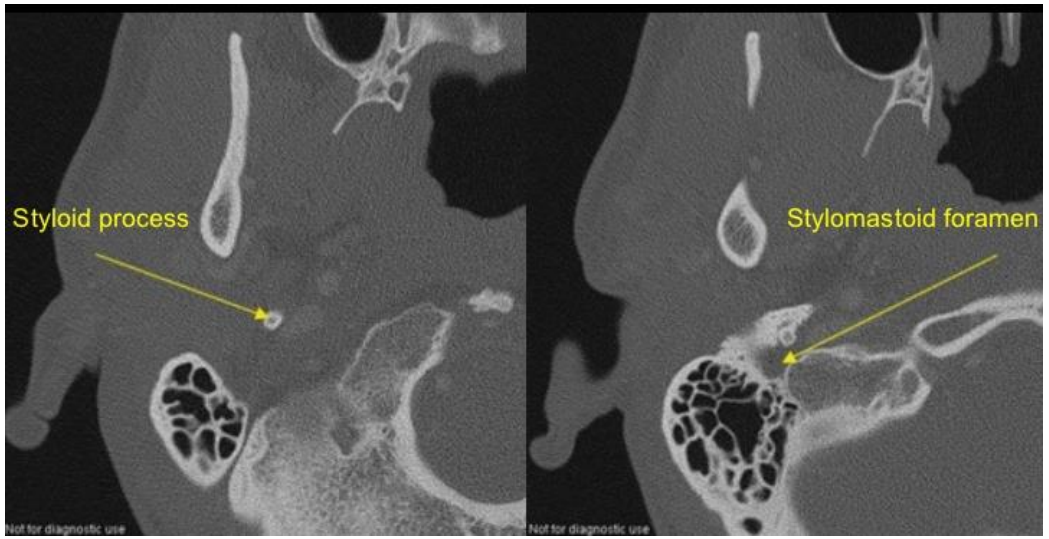




Location of Tumor and PNI

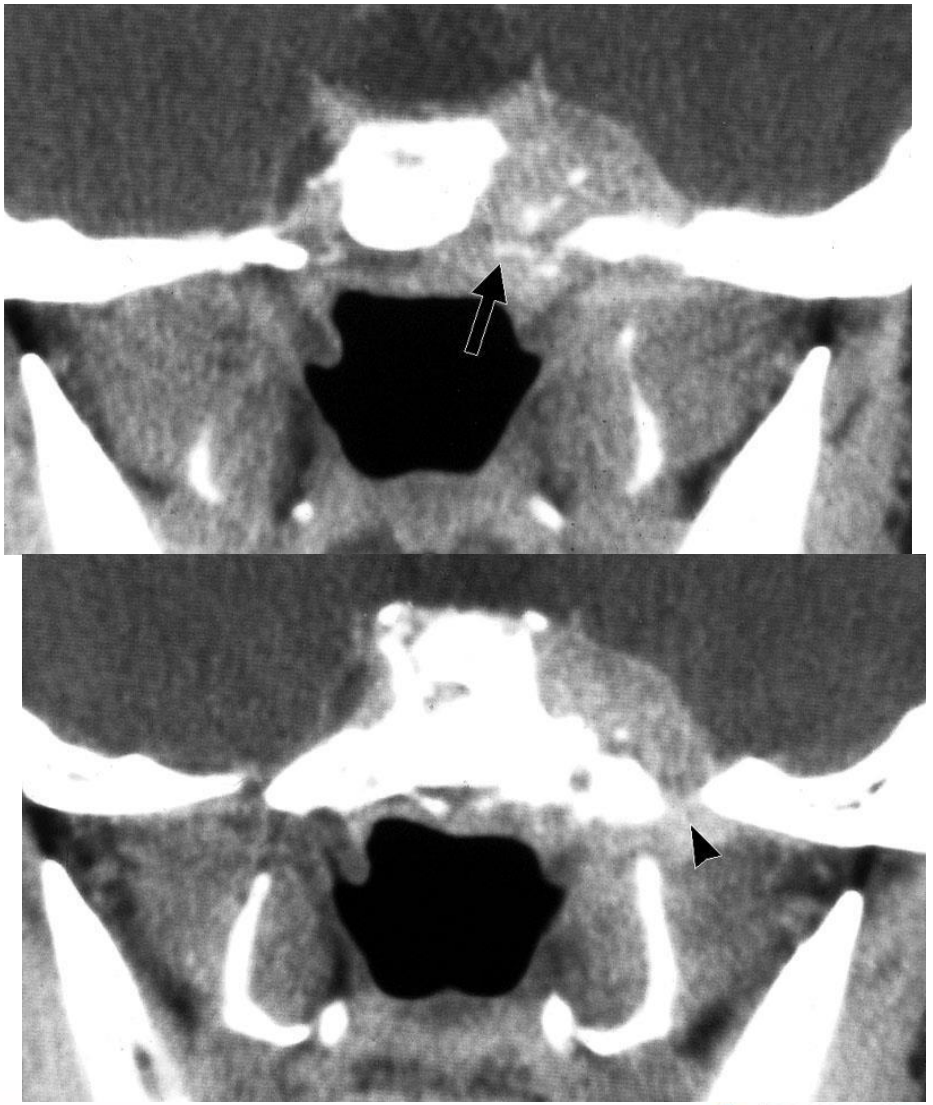
- Ear
  - Facial nerve → Stylomastoid foramen





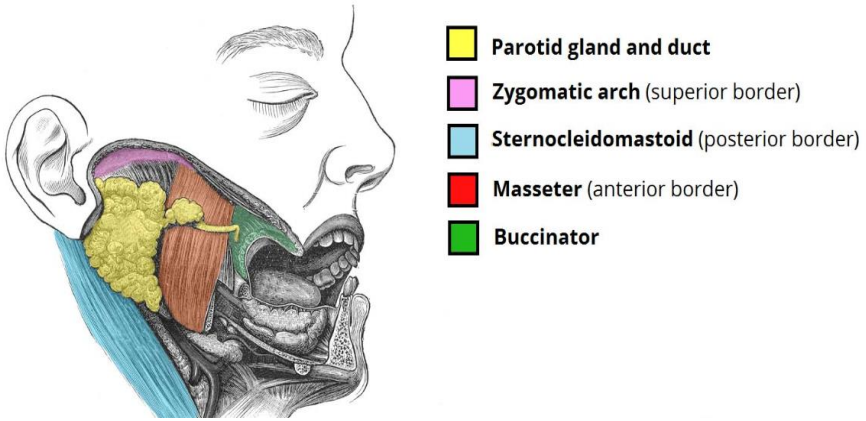
Location of Tumor and PNI

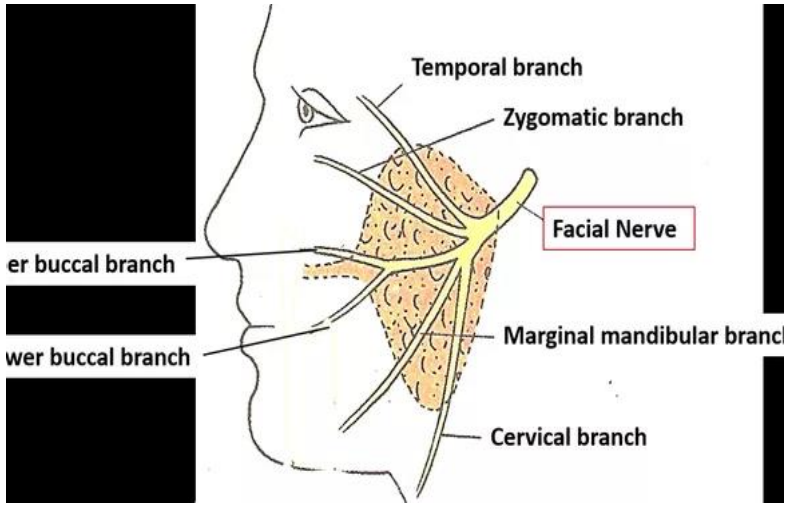
- Nasopharynx
  - Jacod's triad
    - Petrosphenoidal Syndrome
    - CN II-VI
  - Villaret Syndrome
    - Postretroparotid space
    - IX, X, XI, XII and sympathetic nerves



Location of Tumor and PNI

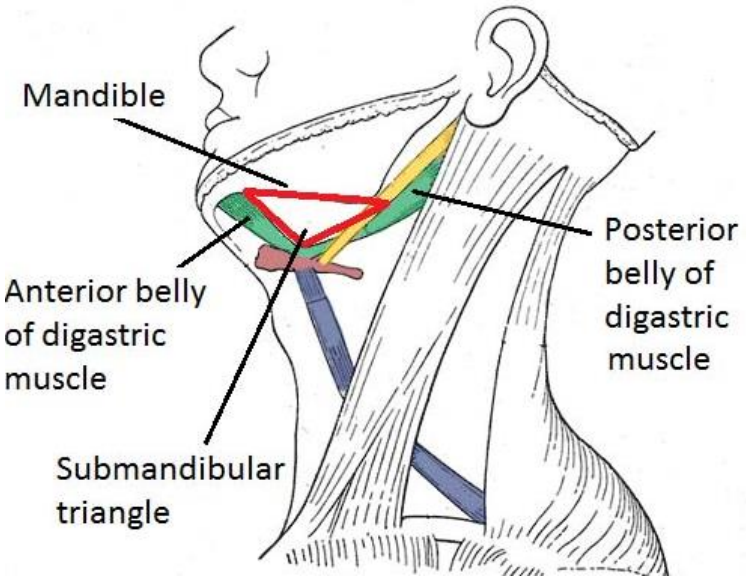
- Parotid Gland
  - Anterior
    - Second maxillary molar
    - Masseter muscle
  - Posterior
    - SCM
    - Mastoid Tip
  - Superior
    - Zygomatic arch
  - Inferior
    - Posterior digastric muscle
- Facial Nerve (VII)
  - Brainstem→ Stylomastoid Foramen→ Separates parotid to deep superficial and deep lobes
  - Retromandibular vein a common landmark for facial nerve
  - Five branches: Temporal, Zygomatic, Buccal, Marginal Mandibular, and Cervical
- Auricotemporal Nerve
  - Branch of V3
  - Innervates parotid gland through parasympathetic control of salivation
  - If damaged by surgery, recovery route to skin causing gustatory sweating (Frey's syndrome)

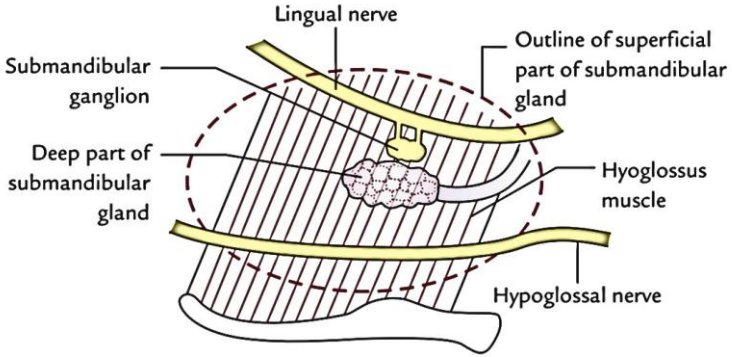




Location of Tumor and PNI

- Submandibular Gland
  - Superior: Inferior body of mandible
  - Anterior: Anterior belly of the digastric muscle
  - Posterior: Posterior bely of the digastric muscle
  - Hypoglossal Nerve
    - Medulla→Hypoglossal Canal→ between ICA/IJV on the carotid sheath
  - Trigeminal Nerve (V3)
    - Foramen Ovale→ Between Medial and Lateral Pterygoid→ Mandibular Foramen→ Lingual nerve
  - Facial Nerve
    - Chorda Tympani innervation





Staging/Degree of PNI

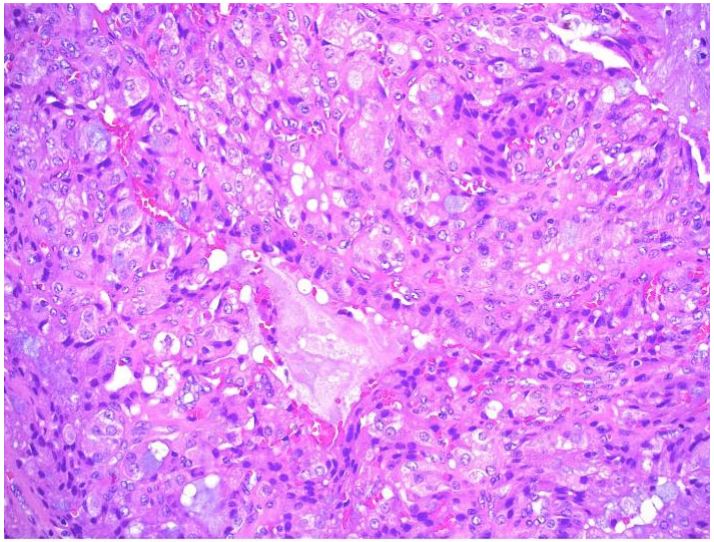
- Worse outcomes with clinical versus microscopic PNI treated with surgery and RT
  - 5 years LC: 87% versus 55% (Garcia-Serra Head Neck 2003)
  - 5 year LC: 90% versus 57% (Jackson Head Neck 2009)
- Cross communication between nerve branches of V and VII
  - 11 patients with PNI of single nerve, recurred with involvement of multiple nerves. Must cover nerve proximally along tract and branches through orbit or masticator space to the base of skull(Gluck IJROBP 2009)

CASE I: SALIVARY CANCER

- Incidence
  - 2,500 cases annually
  - 6% of cases in US
- Classification
  - Major
    - Parotid (75% benign, 25% malignant)
    - Submandibular (50% benign, 50% malignant)
    - Sublingual (25% benign, 75% malignant)
  - Minor
    - Hundreds of mucous-secreting glands beneath mucosal lining of upper aerodigestive tract

CASE I: MALIGNANT SALIVARY GLAND HISTOLOGY

- Mucoepidermoid
  - Most common salivary malignant histology
  - Grade most prognostic
- Adenoid Cystic
  - Most likely to demonstrate PNI
  - Prognosis from best to least is Tubular>cribiform>solid (30% worse)
  - Classic teaching of LN metastasis < 5%
  - Slow growing distant metastasis in up to 50%
  - Late recurrences in > 20 years common
- Adenocarcinoma
  - Nodal metastasis in up to 50-60%
- Actinic cell carcinoma
  - Predominantly in parotid>submandibular
  - Better prognosis in parotid>submandibular
- Carcinoma Ex-pleomorphic
  - Degenerated pleomorphic adenoma
- Salivary duct
  - More common in males (androgen over-expression)
  - Aggressive and higher grade
- Metastasis to salivary gland
  - 5% of salivary malignancies
  - Squamous cell carcinoma and melanoma
- Epithelia-myoepithelial
  - More common in women typically slow growing



Low grade mucoepidermoid carcinoma - 20x

CASE I: WORKUP

- HISTORY AND PHYSICAL
- Size, mobility, and extent of mass
- Meticulous testing of cranial nerves (PNI)
- House Brackman Score
  - Evaluation for degree of facial nerve palsy impairment
    - I (normal)
    - II (Mild dysfunction)
    - III (Moderate Dysfunction)
    - IV (Moderate-severe)
    - V (Severe)
    - IV (Total Paralysis)

Score	Evaluation of Eye
1	Normal
2	>75% Movement, complete closure of eye
3	>50% Movement, resting symmetry
4	<50% Movement, Asymmetric
5	Trace Movement
6	No Movement

Score	Evaluation of Eye Brows, Nasal-labial fold and oral region
1	Normal
2	>75% Movement
3	>50% Movement, resting symmetry
4	<50% Movement, Asymmetric
5	Trace Movement
6	No Movement

Score	Synkinesis
0	No Synkinesis
1	Slight Synkinesis
2	Obvious Synkinesis
3	Disfiguring Synkinesis

Grade	I	II	III	IV	V	VI
Score	4	5-9	10-14	15-19	20-23	>24

CASE I: WORKUP

- Ultrasound
- Fine Needle Aspiration
  - Sensitivity 80%
  - Specificity 95%
- MRI with contrast
  - Evaluation of perineural involvement
- CT chest
  - Malignant histologies
- Dental, nutrition, speech/swallow

STAGING

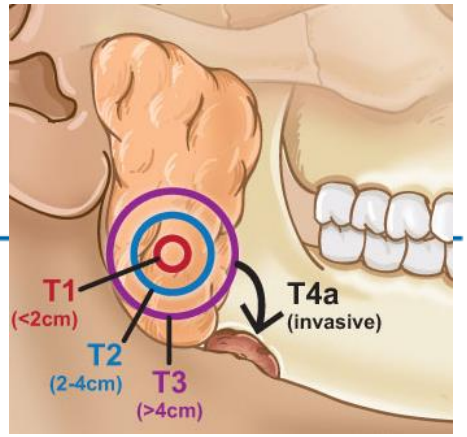


Table 8
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Major Salivary Glands (8th ed., 2017)
(Parotid, Submandibular, and Sublingual)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or smaller in greatest dimension without extraparenchymal extension*
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor larger than 4 cm and/or tumor having extraparenchymal extension*
T4	Moderately advanced or very advanced disease
T4a	Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

Note: Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

Regional Lymph Nodes (N)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastases in any node(s) with clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)

STAGING

Table 8 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Major Salivary Glands (8th ed., 2017)
(Parotid, Submandibular, and Sublingual)

Regional Lymph Nodes (N)

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral lymph node 3 cm or smaller in greatest dimension and ENE(+) *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph node(s), none more than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE(+)

Distant Metastasis (M)

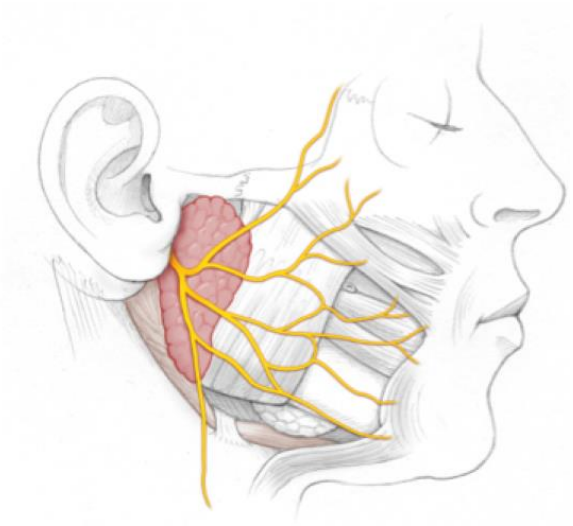
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T0, T1, T2, T3	N1	M0
Stage IVA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

CASE I: Studies

- Surgery
  - Standard of care definitive treatment
    - Superficial parotidectomy for low grade tumors
  - Minimize tumor spillage
  - Preservation of functional cranial nerves
    - Graft if sacrificed
    - Complication of facial nerve palsy of Frey's syndrome (gustatory flushing)
  - Elective nodal dissection optional
    - Parotid: II-IV
    - Submandibular: I-III
  - Clinically positive neck should be dissected
    - Parotid: I-V at risk



CASE I: Studies

- Postoperative Radiation
  - Indications:
    - pT3-4, close or positive margins, high grade, recurrent disease, positive lymph nodes, PNI, LVSI, adenoid cystic histology, and bone invasion
  - In a review (Terhaard, Head and Neck 2005) showed improved 10 year local control after surgery for salivary high risk features
    - T3-4 (18 to 84%)
    - < 5 mm margin (55 to 95%)
    - Positive Margin (44 to 82%)
    - Bone invasion (55 to 86%)
    - PNI (60 to 88%)
  - Improved CSS and LC in stage III-IV patients (Armstrong (Arch Otolaryngol Head Neck Surg)
  - Improved 5 year OS in facial nerve palsy, undifferentiated histology, male, skin involvement (North IJROBP 2990)

CASE I: Studies

- Definitive Radiation
  - Photons
    - 10 year LC of 17 to 57% (Mendehall Cancer 2005, Chen IJROBP 2007, Cinchetti et al,, Wang et al, Laramore et al)
    - Evidence of doses > 70 Gy with better outcomes (Mendenhall Cancer 2005)
    - Use of modern techniques with small retrospective study with IMRT at MSKCC show 5 year LRC of 47% (Spratt Radiol Oncol 2014)
  - Elective Nodal Irradiation
    - Highest incidence in high grade, LVSI, PNI, higher T-stage, and histology with up to up to 15-45% of patients with clinically node negative being node positive at time of resection and therefore should be included in high risk tumors (Xiao NCDB Arch Otol HN Surg 2016; Stennert, Arch Otol HN Surg 2003; Yoo, Korea J Surg Oncol 2015)
  - Neutrons
    - Proposed as means to improve outcome due to higher RBE (> 2.6) compared to photons that may be advantageous in particularly adenoid cystic due to low GF and low doubling time but with significant toxicity and cost
    - RTOG 80-01 compared photon/electron therapy with neutron therapy with 32 patients showing improved LC (17% to 56%) leading to early closure of trial, but NSD In OS but severe late complication in 69% of neutron patients compared to 15% of photons. Criticized for small number of patients, differences in histology, and tumor size imbalances
    - University of Washington showed CSS and LRC of 67% and 59% at 6 years, with 10% G3-4 toxicity at 6 years (Douglas Arch Otolaryngol Head Neck Surg 2003)

CASE I: Studies

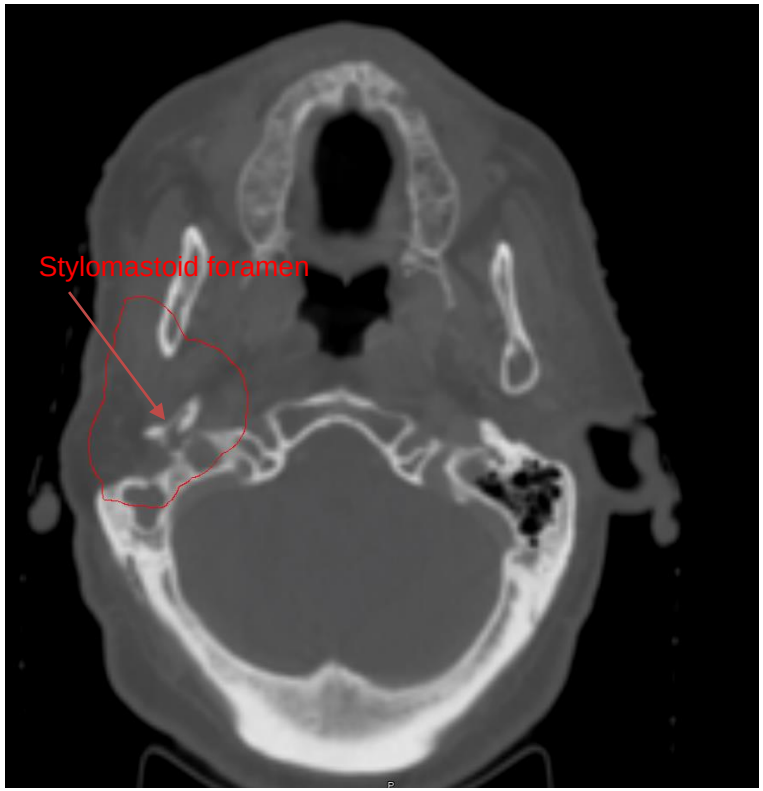
- Chemotherapy
  - No prior prospective trials to date and remains controversial
  - Response rates
    - 35-38% with cisplatin based chemotherapy for recurrent and advanced salivary gland cancer
  - Evidence For:
    - Pair analysis of 24 patients showed improved 3 year OS with chemoradiation from 44 to 83% but increased grade 3 toxicity (Tanvetyanon Arch Otolaryngol Head Neck Surg)
    - Propensity score matched 93 patients of adenoic cystic salivary gland with surgery and postoperative radiation versus chemoradiation (cisplatin based) showed 8 year LRC improved from 67 to 97%) but no difference in OS (Hsieh Radiat Oncol 206)
  - Evidence Against:
    - NCDB analysis of G2-3 salivary gland with one adverse feature after resection showed inferior 5 year OS with chemoradiation compared to RT alone (54 to 28%) (Amini NCDB JAMA Otolaryngol Head Neck Surg 2016)
    - Targeted agents (Imatanib/Lapitanib/Dasatinib) in phase II trials without much benefit (Hotte PMH Jclin Oncol 2005; Agulnik JCO 2007; Wong Ann Oncol 2016)
  - Investigational
    - RTOG 1008 for high risk major salivary gland carcinoma comparing postoperative chemoradiation versus radiation alone

CASE1: SIMULATION

- Position
  - Supine with neck extended
  - Shoulders down
- Immobilization
  - Thermoplastic head and shoulder mask
  - Bite Block and Tongue blade
- Localization
  - Wire Scar
  - Bolus for skin invasion
  - MRI/PET-CT fusion for primary tumor and for nerve localization

CASE 1: TARGET

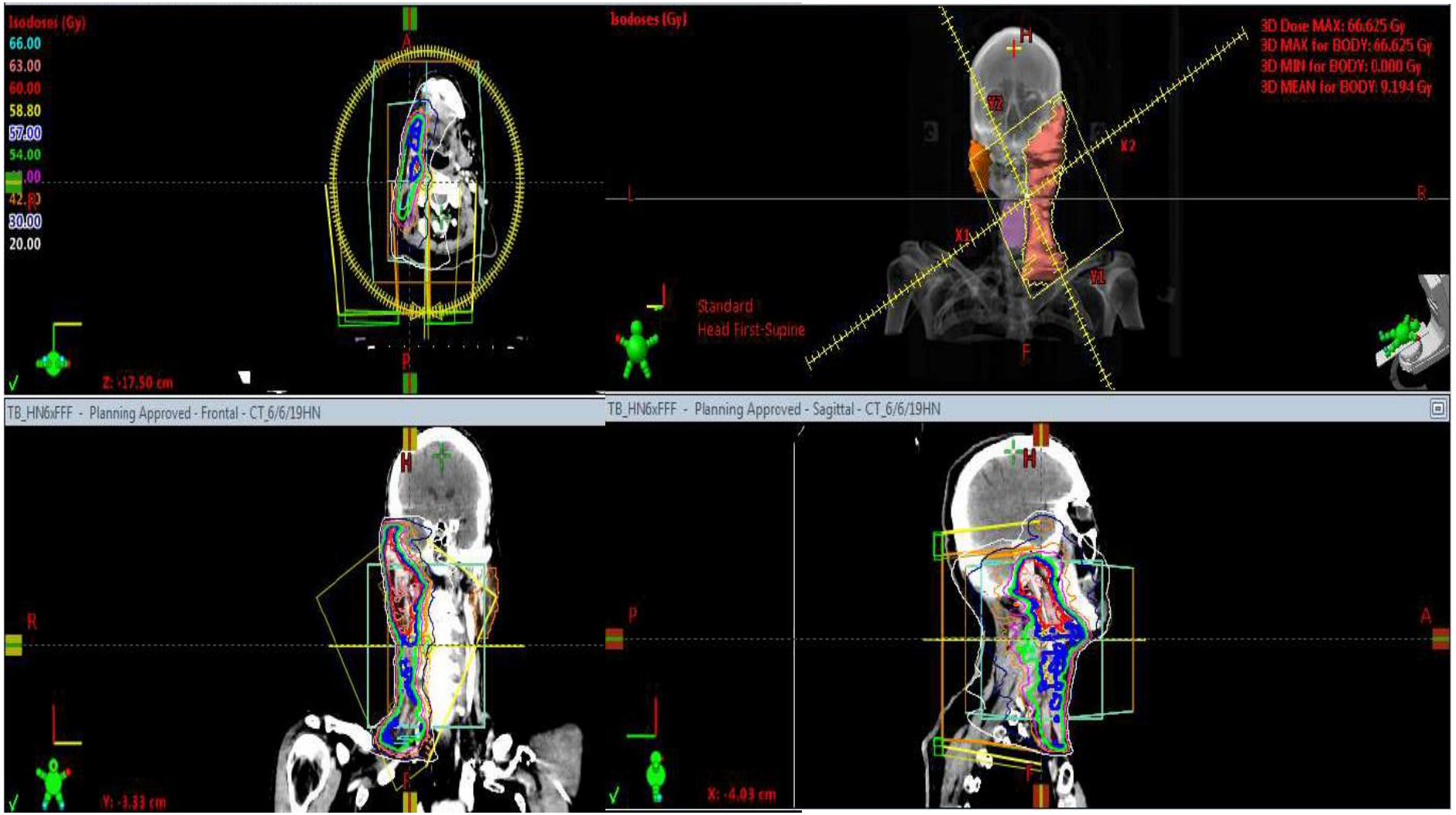
- GTV
  - All gross residual disease and involved nodes
  - Surgical bed
- CTV
  - 70 Gy
    - Gross residual disease
  - 66 Gy
    - Close Positive Margins
    - ENE
  - 60 Gy
    - Primary site, surgical clips, graft, edema, and areas of involved nodal disease
    - Parapharyngeal space/retrostyloid (T3-T4)
    - CN V3, VII, XII to base of skull foramina (Adenoid cystic)
    - VII treated through stylomastoid foramen to base of skull (Parotid with PNI)
  - 54 Gy
    - Node negative ipsilateral cervical neck, supraclavicular neck if necessary
    - At risk nerves back to base of skull
- PTV
  - CTV + 3 mm with daily IGRT imaging



CASE 1: TECHNIQUE

- IMRT
  - Recommended for large postoperative beds or extended neck coverage
- Conventional
  - Wedged pair photon beams
  - Mixed photon/electron beam
  - Angle Obliquely to keep off spinal cord
  - Superior half-beam block to match primary field

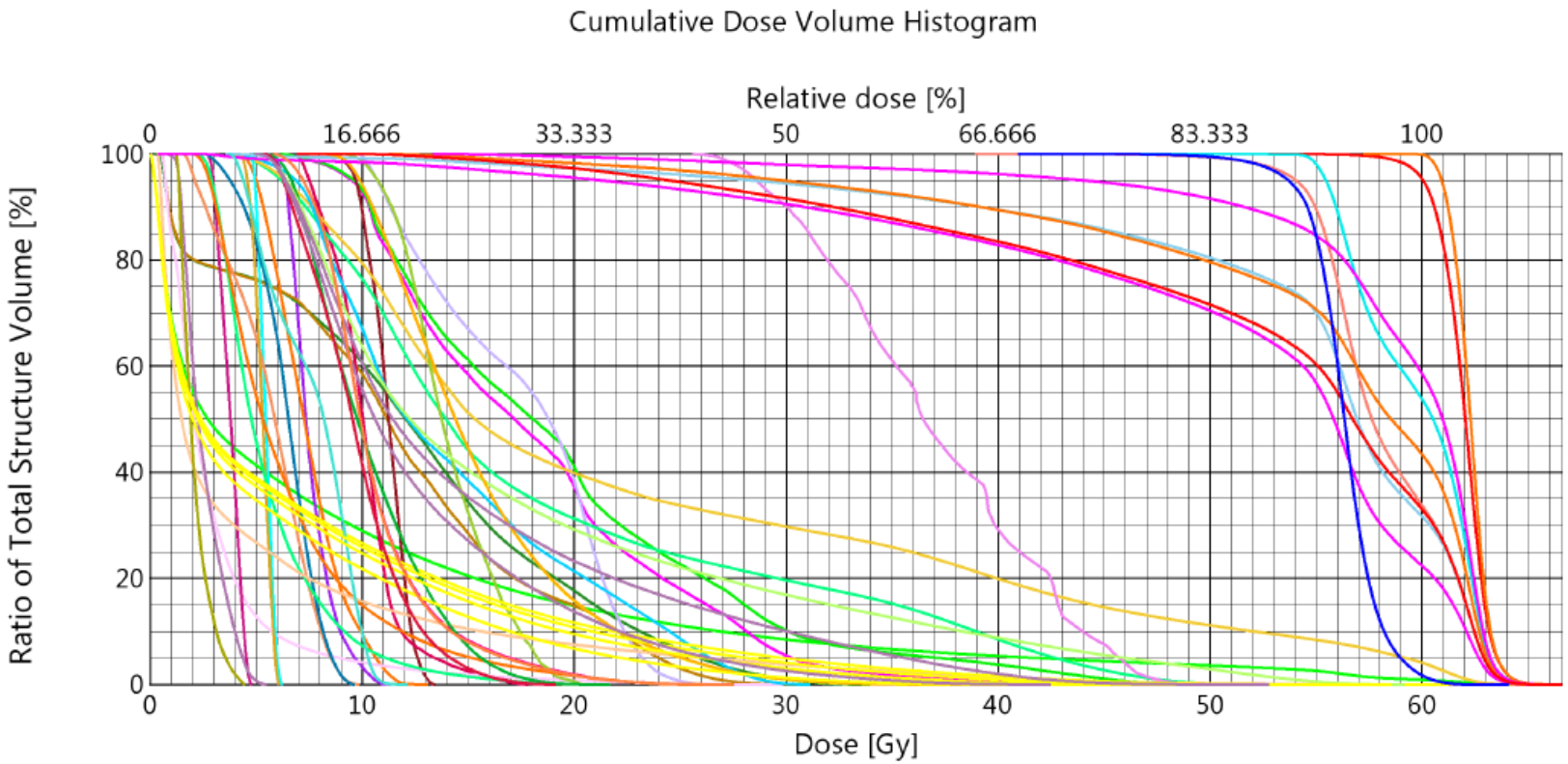
CASE 1: IMRT PLAN



OAR (Recommended)

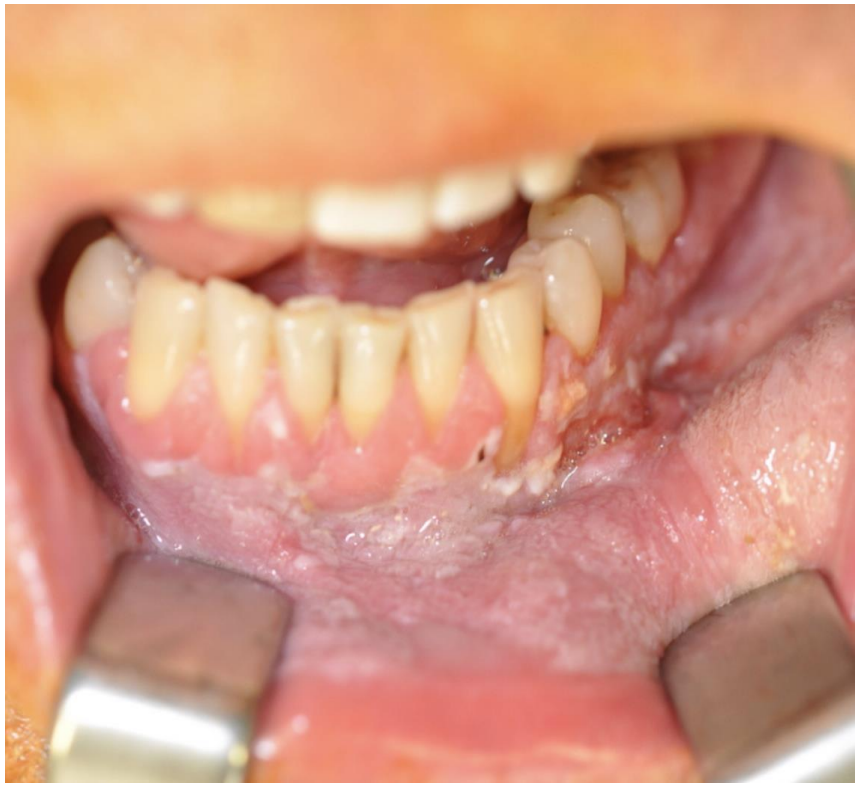
- Brainstem: max 54 Gy
- Optic chiasm: max 45 Gy
- Cochlea: max 45 Gy
- Mandible: limit V70 < 1%
- Temporal lobe: Max < 60
- Optic Nerve : Max < 54 Gy
- Retina: Max < 45 Gy
- Contralateral Parotid: Mean < 26 Gy
- Submandibular Gland: Mean < 39 Gy
- Pharyngeal Constrictors: Mean < 45 Gy
- Middle Ear: Max < 50 Gy
- Larynx: Mean < 40 Gy
- True Vocal Cords: Max < 25 Gy
- Temporal Mandibular Joint: Mean < 45 Gy
- Lacrimal Gland: V30< 50%
- Lens: Max < 10 gy

CASE 1: DVH


Cumulative Dose Volume Histogram
Relative dose [%]
0
16.666
33.333
50
66.666
83.333
100
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
10
20
30
40
50
60
Dose [Gy]

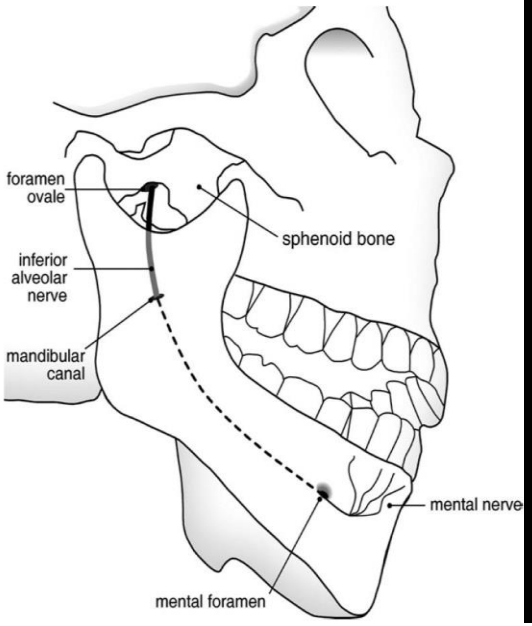
CASE II: Oral Cavity

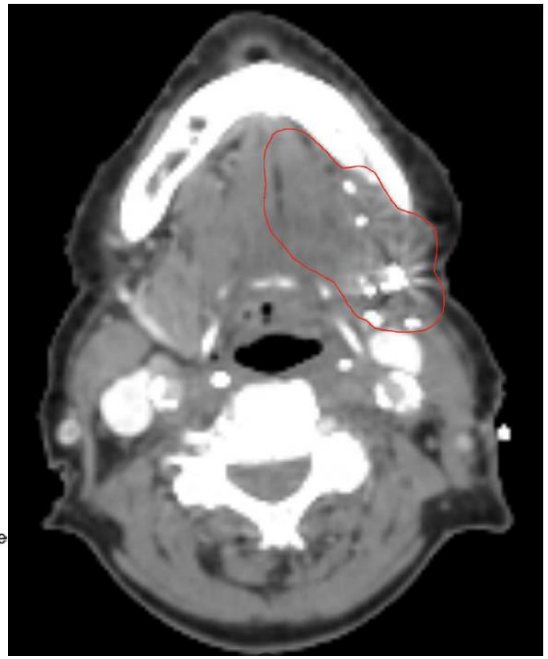
- 65 year-old male s/p surgery for T4N0 (4.5 cm) SCC of left gingiva region with negative margins, high grade, invasion of the mandible, with significant PNI



Case II: Oral Cavity

- Patient was treated with IMRT
  - 60 Gy to the primary resection bed
  - 54 Gy to the bilateral neck and nerve tracts
    - Covered the inferior alveolar nerve from retrograde pathway→ Mandibular Foramen→V3→ Foramen ovale of the base of skull





Follow-up

- H&P
  - Every 1–2 months for year 1
  - Every 3 months for years 2–3
  - Every 6 months for years 4–5,
  - Annually after 5 years
- MRI at 6 months and again as indicated
- TSH every 6-12 months if neck irradiated

Suggested Atlas for RT coverage of head and neck cancers with PNI

- Mouradet al, Clinical validation and applications for CT-based atlas for contouring of the lower cranial nerves for head and neck cancer radiation therapy. Oral Oncology 2013; 16: 956-963.
- Koet al, A contouring guide for head and neck cancers with perineuralinvasion. Practical Radiation Oncology 2014; 4: 247-258.

Conclusion

- Perineural invasion for head and neck cancers is associated with high risk of local regional and base of skull recurrence
- Postoperative RT should be offered in cases of PNI with coverage of at risk nerves to the base of skull

References

- “Chapter 14: Salivary Gland Carcinomas.” *Clinical Radiation Oncology: Indications, Techniques, and Results*, by William Small et al., John Wiley & Sons, Inc., 2017, pp. 288–297.
- “Chapter 10: Salivary Gland Tumors.” *Handbook of Evidence-Based Radiation Oncology*, by Eric K. Hansen and Mack Roach, Springer, 2018.
- “Chapter 14: Salivary Gland Tumors.” *Essentials of Clinical Radiation Oncology*, by Matthew C. Ward et al., Demos Medical, 2018.
- “National Comprehensive Cancer Network: Head and Neck Cancers.” *NCCN*, www.nccn.org/.

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