Nasopharyngeal carcinoma

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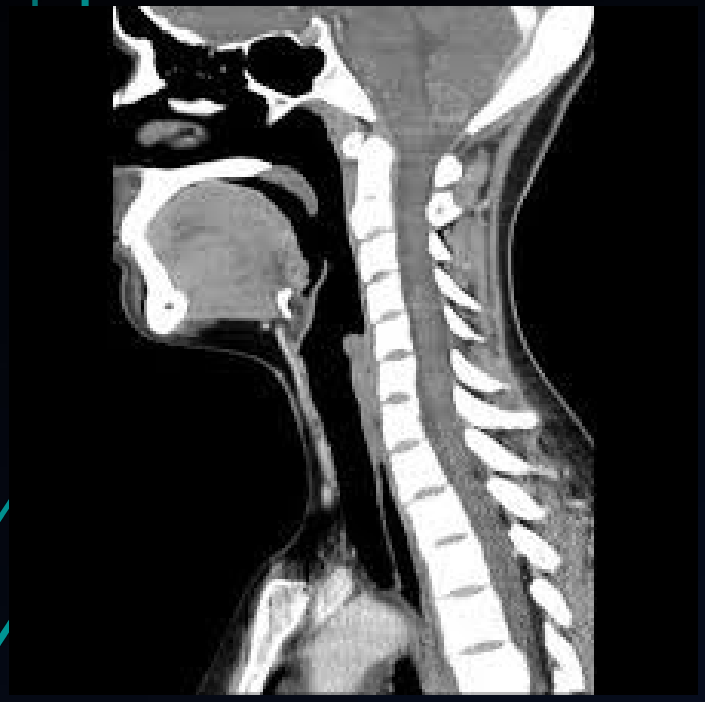
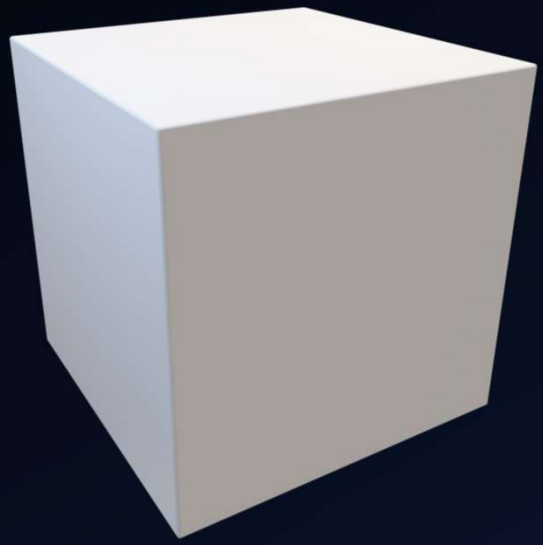
Nothing to disclose

Content

- Anatomical consideration
- Epidemiology & Natural history
- Staging
- Treatment modality
- Treatment complication
- Follow up
- Role of surgery



Skull base (basisphenoid and clivus)

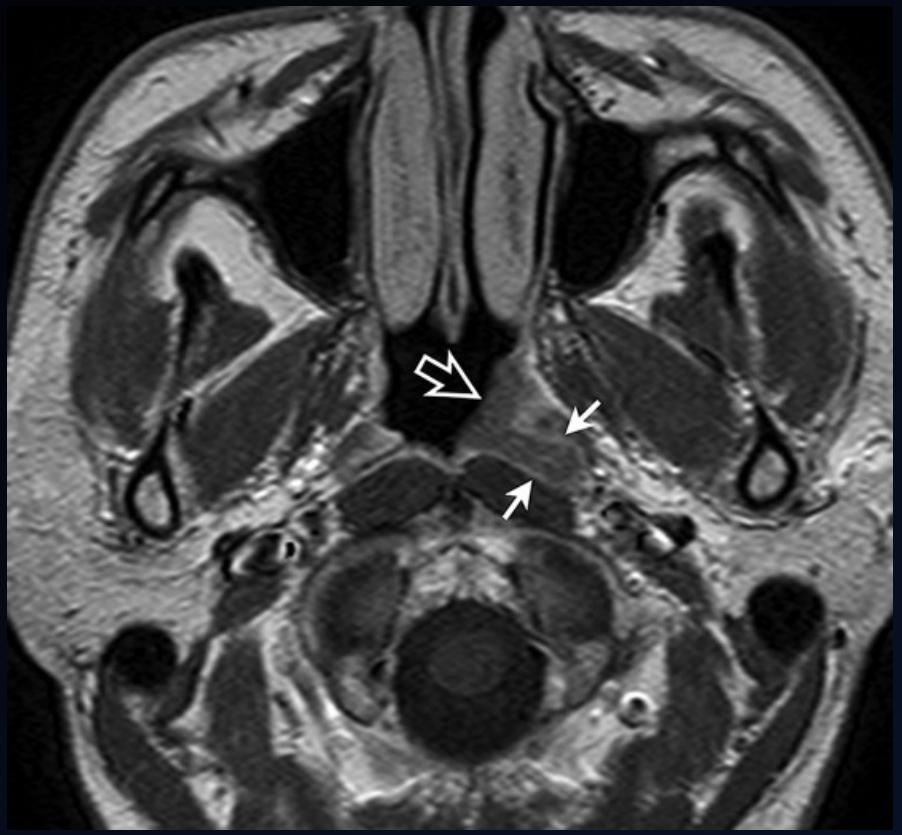


Prevertebral muscle C1-2

Post choana

Soft palate level

Related fascial space

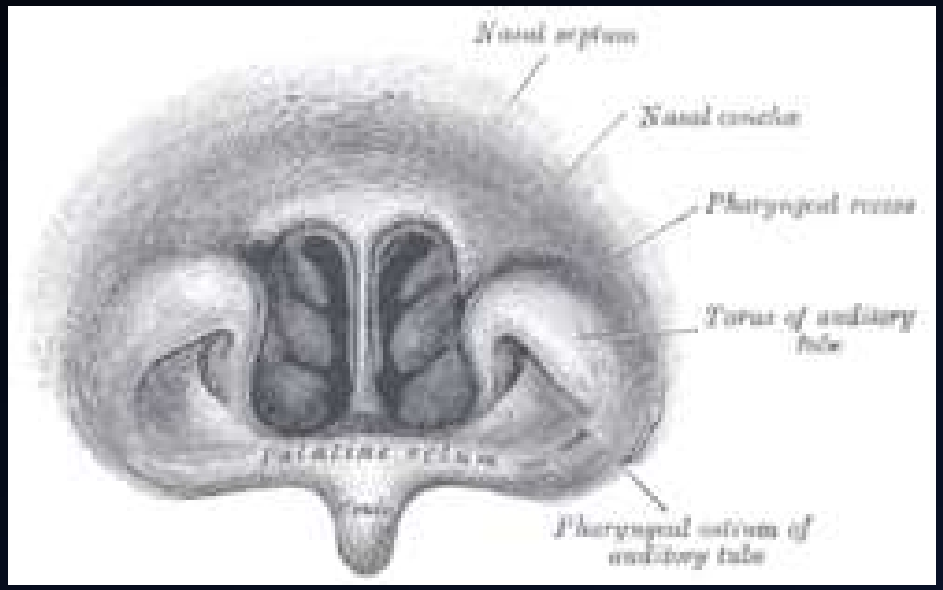


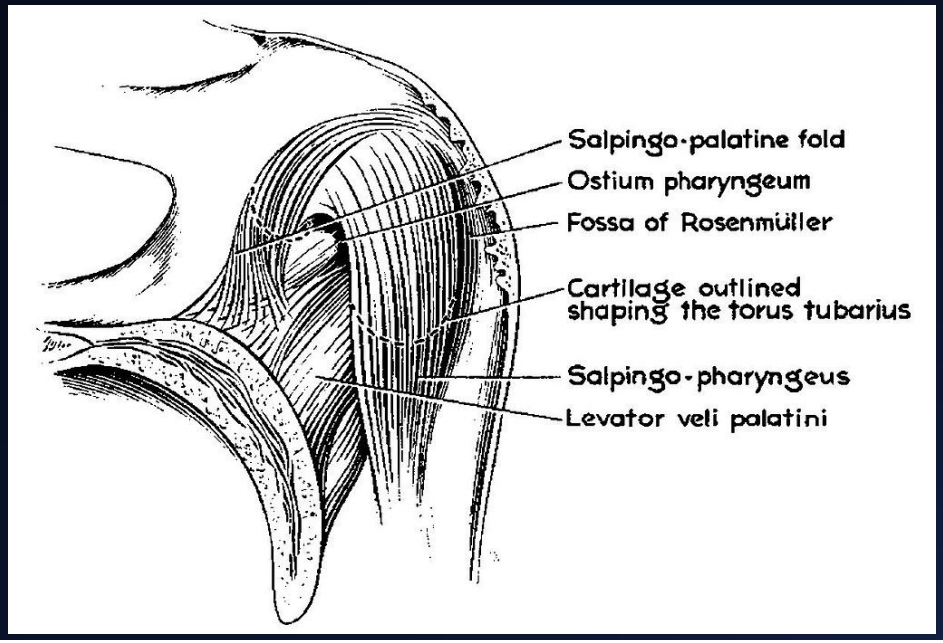
- Pharyngeal mucosal sp.
- Parapharyngeal sp.
- Retropharyngeal sp.
- Danger sp.
- Prevertebral sp.
- Carotid sp.
- Masticator sp.

Lateral wall anatomy

- Torus tubarius
- Rosenmuller fossa
- Eustachain tube

- Salpingopharyngeal fold
- Salpingopalatine fold
- Pharyngeal recess





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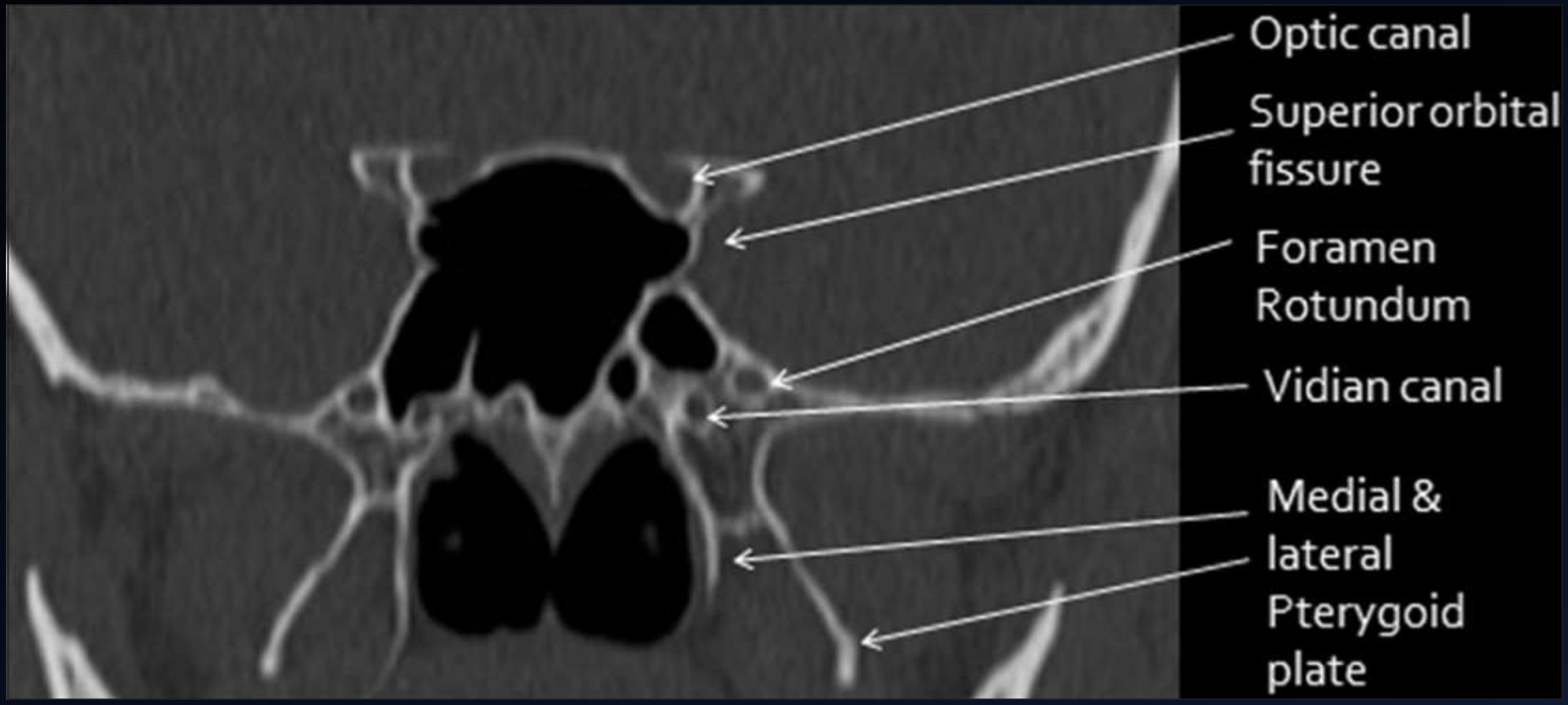
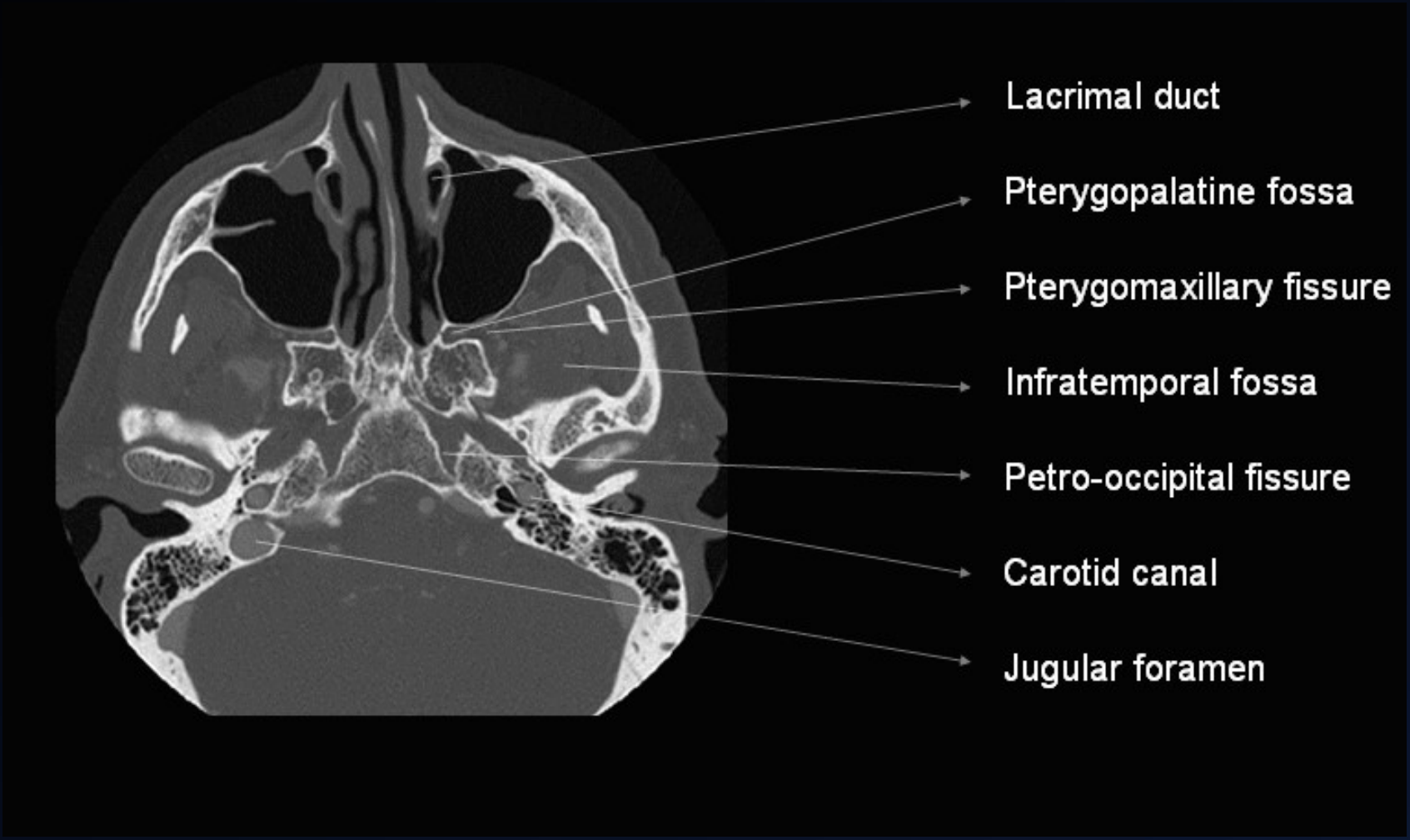
Related cranial nerve

- CN I : Roof of nose
- CN II : optic foramen
- CN III / V1 : superior orbital fissure
- CN V2 : foramen rotundum
- CN V3 : foramen ovale
- CN IX / X / XI : Jugular foramen


Optic canal
Superior orbital fissure
Foramen Rotundum
Vidian canal
Medial & lateral Pterygoid plate


Lacrimal duct
Pterygopalatine fossa
Pterygomaxillary fissure
Infratemporal fossa
Petro-occipital fissure
Carotid canal
Jugular foramen

Epidermiology

- Per 100,000 peoples
  - 80 cases in SEA , north Africa
  - 20 cases in Alaska , Greenland
  - 0.5 in USA
- Ethnical predisposition
  - Cantonase(China)
  - Nagas(india)
  - Inuits(Arctic)
  - Bidayuh(Borneo)
- M > F
- Peak age 50-60 yr

Pathogenesis

Possible etiology

- Carcinogen
  - Salted fish
  - N-nitrosamine
  - Preserved food, Formaldehyde, herbal tea
- Tobacco & Alcohol → controversial
- Viral infection

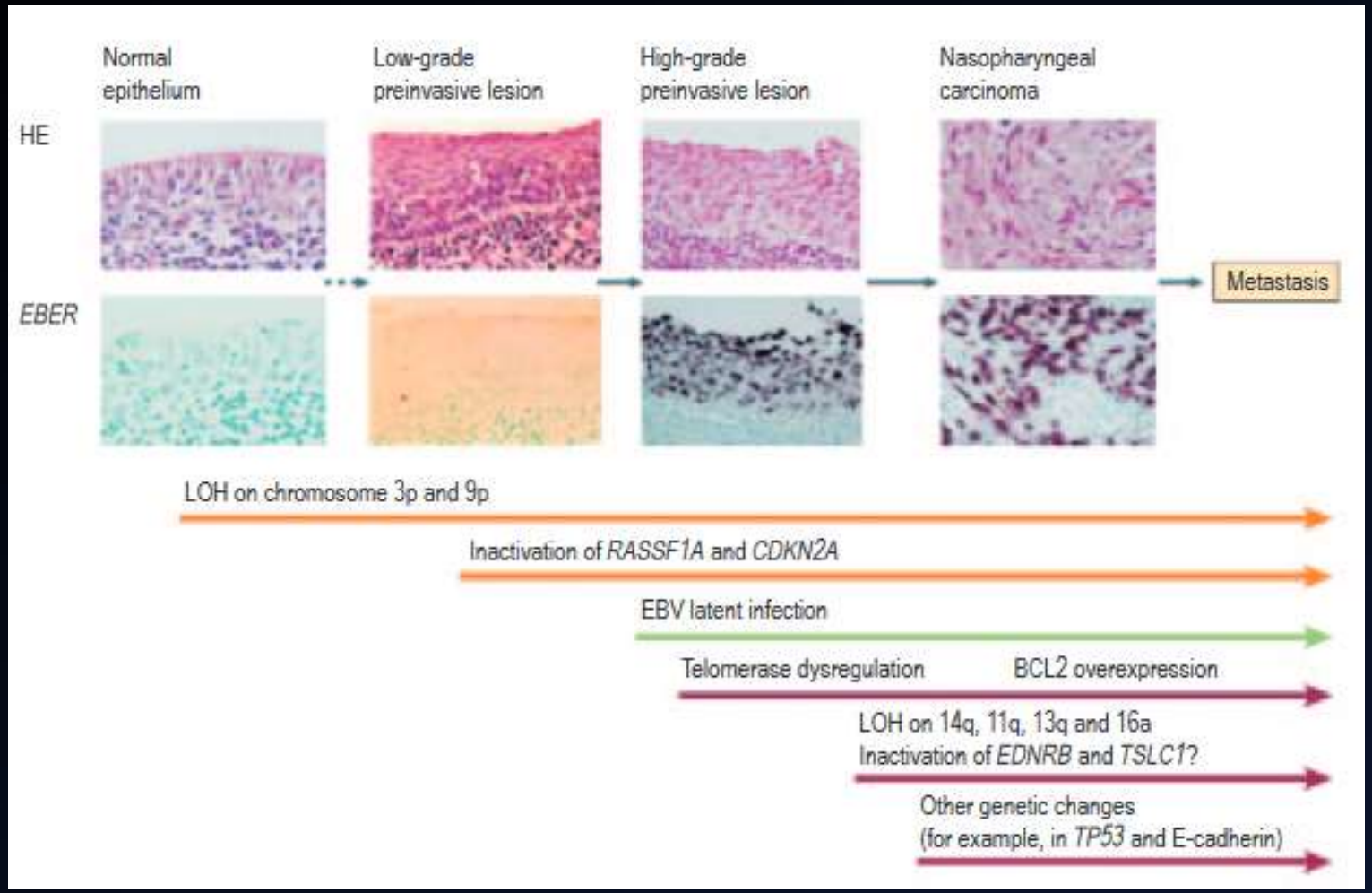
	Epidemiology	Overall survival	Local control	Distant metastasis-free survival
HPV-negative/EBV-positive	Endemic regions	Most superior	Most superior	Lowest
HPV-positive/EBV-negative	Non-endemic regions	Moderate	Moderate	Moderate
HPV-negative/EBV-negative	Non-endemic regions	Lowest	Lowest	Moderate

HPV=human papillomavirus. EBV=Epstein-Barr virus.

Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. Lancet. 2016 Mar 5;387(10022):1012-1024. doi: 10.1016/S0140-6736(15)00055-0. Epub 2015 Aug 28. Review. PubMed PMID: 26321262.

EBV and NPC

- Identified since 1964
- 1st viral that prove to cause human cancer
- Detected in NPC tumor cell
- Associate with undifferentiated carcinoma


Normal epithelium
Low-grade preinvasive lesion
High-grade preinvasive lesion
Nasopharyngeal carcinoma
HE
EBER
Metastasis
LOH on chromosome 3p and 9p
Inactivation of RASSF1A and CDKN2A
EBV latent infection
Telomerase dysregulation
BCL2 overexpression
LOH on 14q, 11q, 13q and 16a
Inactivation of EDNRB and TSLC1?
Other genetic changes
(for example, in TP53 and E-cadherin)

EBV for….

- Screening?
- Prognosis prediction
- Treatment response evaluation
- Surveillance

Clinical presentation

- Neck mass
  - Level Va , II
- Nasal symptom
- Otological symptom
- Neurological symptom
  - Cranial n. VI
- Ocular symptom
- Related syndrome

Radiological finding : Primary

- Enhancing & infiltrative mass
  - Deep mucosal white line
  - Signal asymmetry
  - Depth of thickened mucosa
  - Extension

Radiological finding : Nodal

- Size criteria
  - > 8 mm : retropharyngeal
  - > 15 mm : level Ib , II
  - > 10 mm : other level

- Round
- Multiple
- Necrosis
- ECE

Pathological study

NORMAL

- stratified squamous epithelium
- Ciliated pseudost columnar
- Respiratory-type epithelium
- Lymphoid
- Seromucinous gland

CARCINOMA

- Keratinizing SCCA (WHO – I)
- Non-Keratinizing
  - Differentiated (WHO – II)
  - Undifferentiated (WHO – III)
- Basaloid SCCA

Ker. VS Non-ker. carcinoma

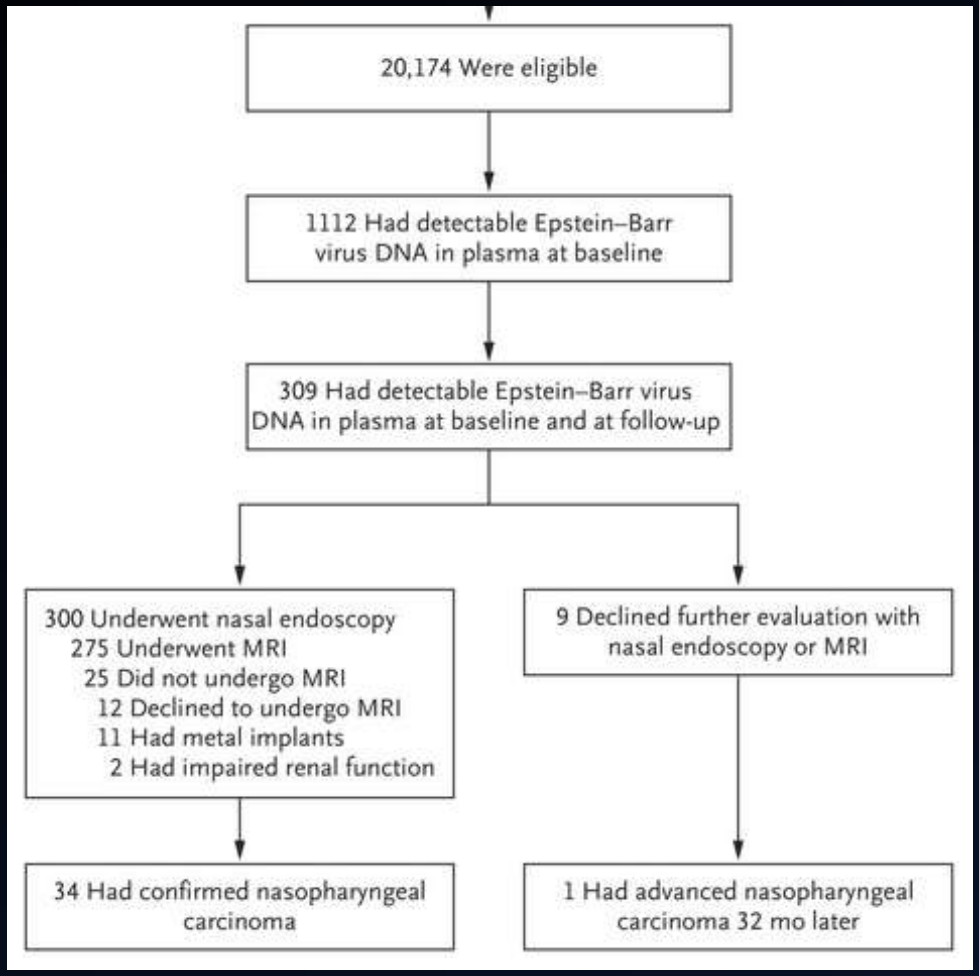
- Found in Western
- Not associate with EBV
- Poorer prognosis

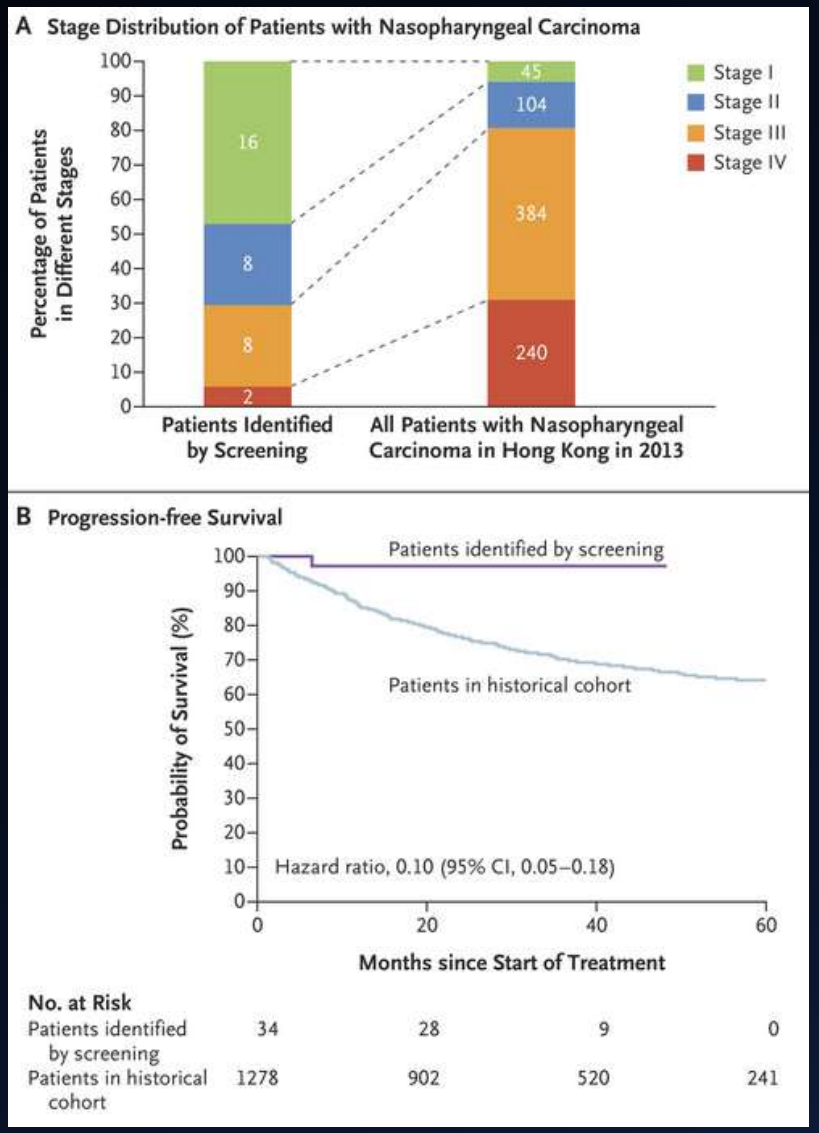
Screening??

Nasopharyngoscope

EBV – blood test

Screening with EBV





N Engl J Med 2017; 377:513-522

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Pre-treatment evaluation

- Complete physical examination
- Essential imaging
  - MRI / CT
- Metastasis workup
  - Bone scan
  - CT chest / abdomen
  - PET/CT
- Dental evaluation
- Hearing evaluation
- Thyroid function
- EBV study (EBV viral load)

- H&P[a,b] including a complete head and neck exam; mirror examination as clinically indicated
- Nasopharyngeal fiberoptic examination
- Biopsy of primary site or FNA of the neck
- MRI with contrast of skull base to clavicle ± CT of skull base/neck with contrast to evaluate skull base erosion
- Imaging for distant metastases with FDG-PET/CT and/or chest CT with contrast
- Consider Epstein-Barr virus (EBV)/DNA testing[e]
- As clinically indicated:
  - Dental,[c] nutritional, speech and swallowing, and audiology evaluations[d]
  - Consider ophthalmologic and endocrine evaluation

Multidisciplinary consultation as clinically indicated

Staging ; What's new from AJCC 2010 → 2017

1. Add T0 for EBV – carcinoma of unknown primary
2. No more masticator / infratemporal fossa
   → use muscle involvement instead
3. Add prevertebral muscle involvement as T2
4. No supraclavicular fossa N3
   → use 'lower neck' + size
5. Move T4,N3 to stage IVa
6. Move M1 to stage IVb

A comparison of staging systems

Classification	American Joint Committee on Cancer[24]	2002/1997 American Joint Committee on Cancer[29,30]	Ho[27]	2008 Chinese[28]
T1	Confined to nasopharynx, or extends to oropharynx and/or nasal cavity	Confined to nasopharynx	Confined to nasopharynx	Confined to nasopharynx
T2	With parapharyngeal extension	Soft tissue invasion a. Without parapharyngeal extension b. With parapharyngeal extension	Nasal fossa, oropharynx, muscle, or nerves below base of skull	Nasal cavity, oropharynx, parapharyngeal extension
T3	Bony or paranasal sinus extension	Bony or paranasal sinus extension	a. Bone involvement below base of skull b. Involves base of skull c. Cranial nerves d. Orbits, laryngopharynx, or infratemporal fossa[a]	Skull base or medial pterygoid extension
T4	Intracranial extension, or cranial nerve or infratemporal fossa,[a] hypopharynx, or orbital involvement	Intracranial extension, or cranial nerve or infratemporal fossa,[a] hypopharynx, or orbital involvement	—	Cranial nerves, paranasal sinuses, masticator space[a] (excluding medial pterygoid muscles), intracranial (cavernous sinus, dural meninges) extension

Classification	American Joint Committee on Cancer[24]	2002/1997 American Joint Committee on Cancer[29,30]	Ho[27]	2008 Chinese[28]
N1	Unilateral, ≤6 cm and/or unilateral or bilateral retropharyngeal ≤6 cm	Unilateral, ≤6 cm	Upper neck above thyroid notch	a. Retropharyngeal b. Unilateral level Ib, II, III, and Va or ≤3 cm
N2	Bilateral, ≤6 cm	Bilateral, ≤6 cm	Below thyroid notch above line joining end of clavicle and superior margin of trapezius muscle	Bilateral level Ib, II, III, and Va or >3 cm or with extranodal spread
N3	a. >6 cm node b. Supraclavicular involvement	a. >6 cm node b. Supraclavicular involvement	Supraclavicular fossa[b] or skin involvement	Level IV or Vb involvement

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Carcinoma *in situ*
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/ or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage

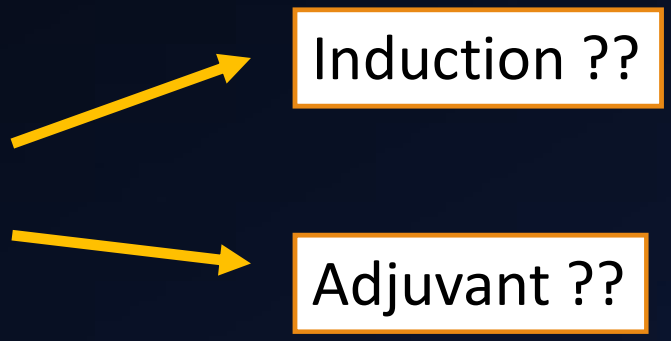
N2 Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage

N3 Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T0, T1	N1	M0
	T2	N0, N1	M0
Stage III	T0, T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Treatment

- Radiation is the key
  - Intensity-modulated radiation therapy (IMRT)
  - Radiosensitive tumor
  - Surround by vital structure
- Chemotherapy
  - Add control outside local therapy
  - Add response to radiation
  - Al-Sarraf ; Intergroup study 0099 ; 1998
  - Cisplatin / Carboplatin / 5-Fluorouracil



A comparison of the major concurrent chemoradiotherapy randomized trials

Study	No. Patients	Stage	Randomization	Disease-free Survival (%), 5 y	*P* Value	Overall Survival (%), 5 y	*P* Value
Intergroup study 0099,[43] 1998	150	AJCC 1992 stage III: T3N0; T1-3N1M0	70 Gy/7-8 wk	29	<.001	37	.005
		AJCC 1992 stage IV: T4N0-1; any TN2-3M0	70 Gy/7-8 wk with cisplatin, followed by 3 cycles of cisplatin/5-FU	58		67	
Chan et al,[44] 2002; Chan et al,[45] 2005	350	Ho system N2-3 or any nodes ≥4 cm	66 Gy/6.5 wk ± 10–20 Gy boost	52	NS	59	.065
			66 Gy/6.5 wk ± 10–20 Gy boost with cisplatin	60		70	
Lin et al,[46] 2003	284	AJCC 1992: III-IV (M0)	70–74 Gy/6–7 wk	53	.0012	54	.0022
			70–74 Gy/6–7 wk with infusional cisplatin/5-FU × 2	72		72	
Wee et al,[47] 2005	221	AJCC 1997: stage III or IV; WHO type 2 or 3	70 Gy/7 wk	53 (3 y)	.01	65 (3 y)	.01
			70 Gy/7 wk with infusional cisplatin, followed by 3 cycles of cisplatin/5-FU	72 (3 y)		80 (3 y)	
Lee et al,[48] 2005	348	AJCC 1997: T1-4N2-3M0; WHO type 2 or 3	>66 Gy/7–8 wk	62	.027	78	.97
			>66 Gy/7–8 wk with cisplatin, followed by 3 cycles of cisplatin/5-FU	72		78	

Post treatment protocol

- Imaging
- Nasopharyngoscope
  - ± Blind biopsy
- Complication screening and treatment
- EBV viral load

Treatment complication

- Mucositis
- Xerostomia
- Hearing loss
  - Conductive
  - Sensorineural
- Nasal complication
  - Synechia
  - Sinusitis
- Pharyngeal complication
  - Velopharyngeal stenosis
  - Swallowing disorder
- Ocular complication
  - Radiation induced optic neuropathy
  - Radiation retinopathy
  - Ocular neuromyotonia
- Neurological complication
  - RICNP
  - RIBP
  - Lhermitte’s sign
- Endocrinological complication
  - Hypopituitarism
  - Hypothyroidism

Recurrent / Residual treatment option

- Primary site
  - Surgery
    - Open / conventional surgery
    - Endoscopic nasopharyngectomy
    - Robotic nasopharyngectomy
  - Re-radiation
    - Boost external beam RT
    - Brachytherapy

Contraindication of surgery

- Skull base erosion
- Cavernous sinus involvement
- PPS extension
- Carotid involvement
- Paraspinal involvement
- Prove distance metastasis

Recurrent / Residual neck treatment option

- Isolated neck failure < 10%
- Surgery : RND , MRND
- No role of Re-radiation after salvage neck disease

Metastasis disease

- Oligometastatis → curative aim & definite treatment
- Cisplatin + 5-FU : standard 1st line treatment

Other options

- Molecular / Targeted therapy
  - Anti EGFR / VEGF
- Immunotherapy