Nasopharynx

Benjamin H. Lok, Jeremy Setton, Felix Ho, Nadeem Riaz, Shyam S. Rao, and Nancy Y. Lee

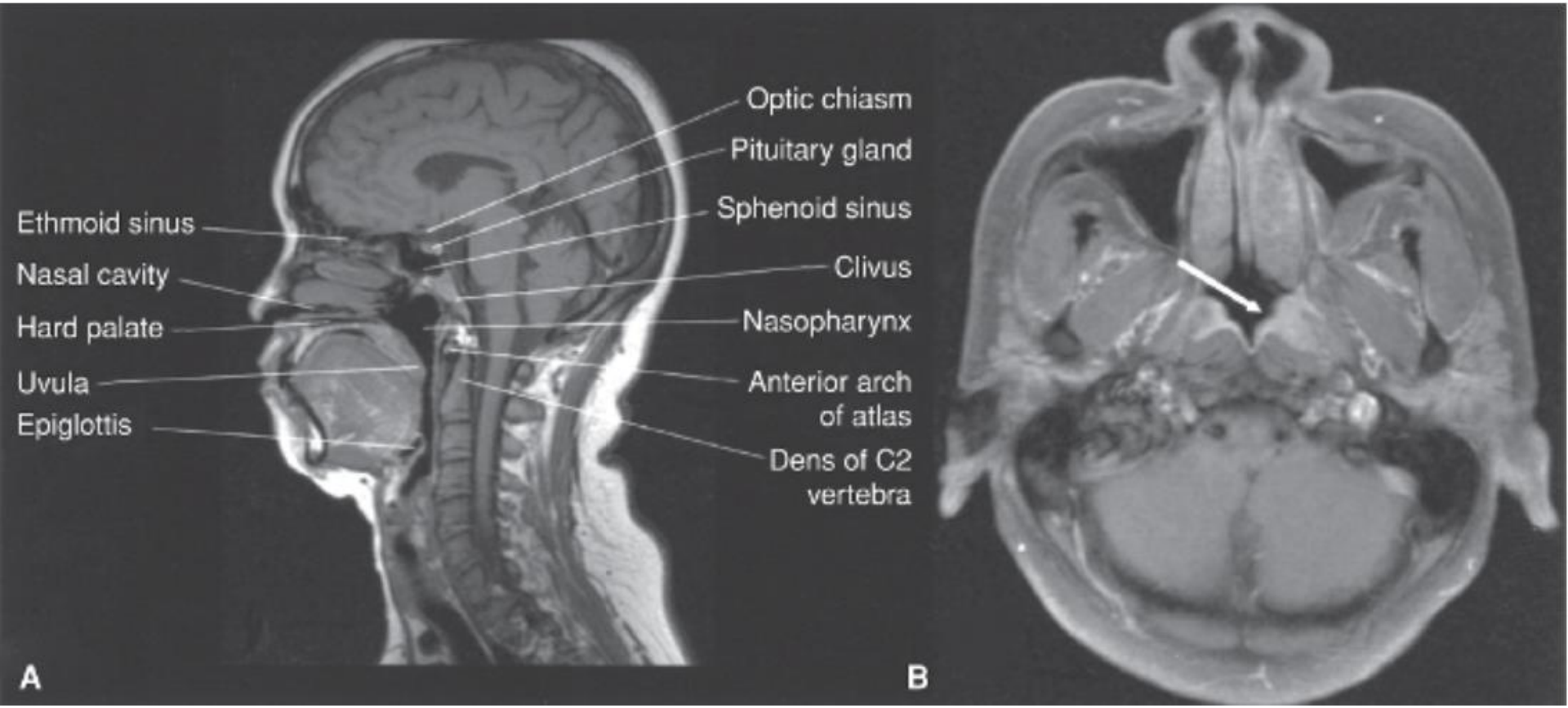
學習目標　放射治療在鼻咽癌的應用

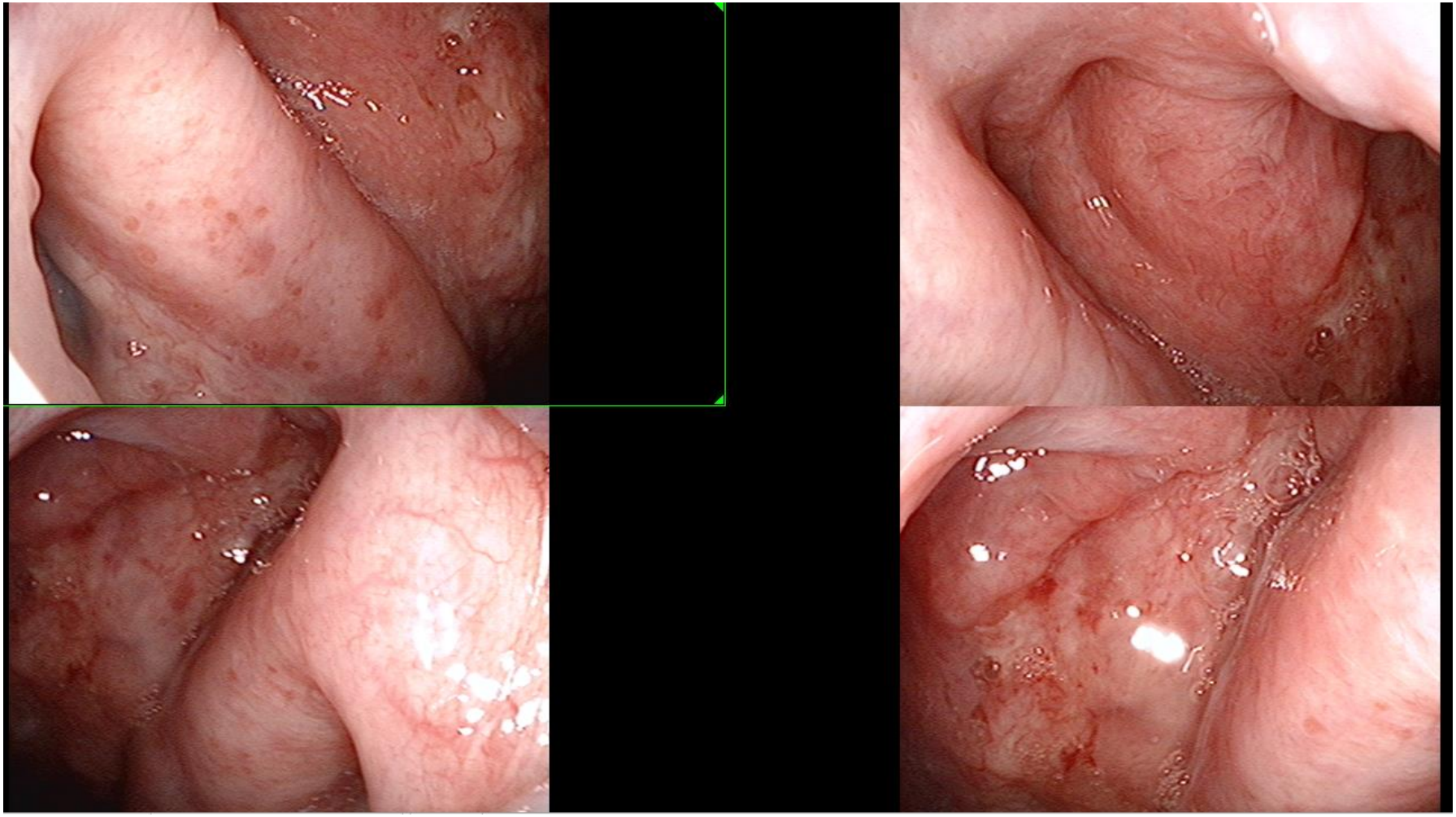
製作人　　范兆岳 醫師

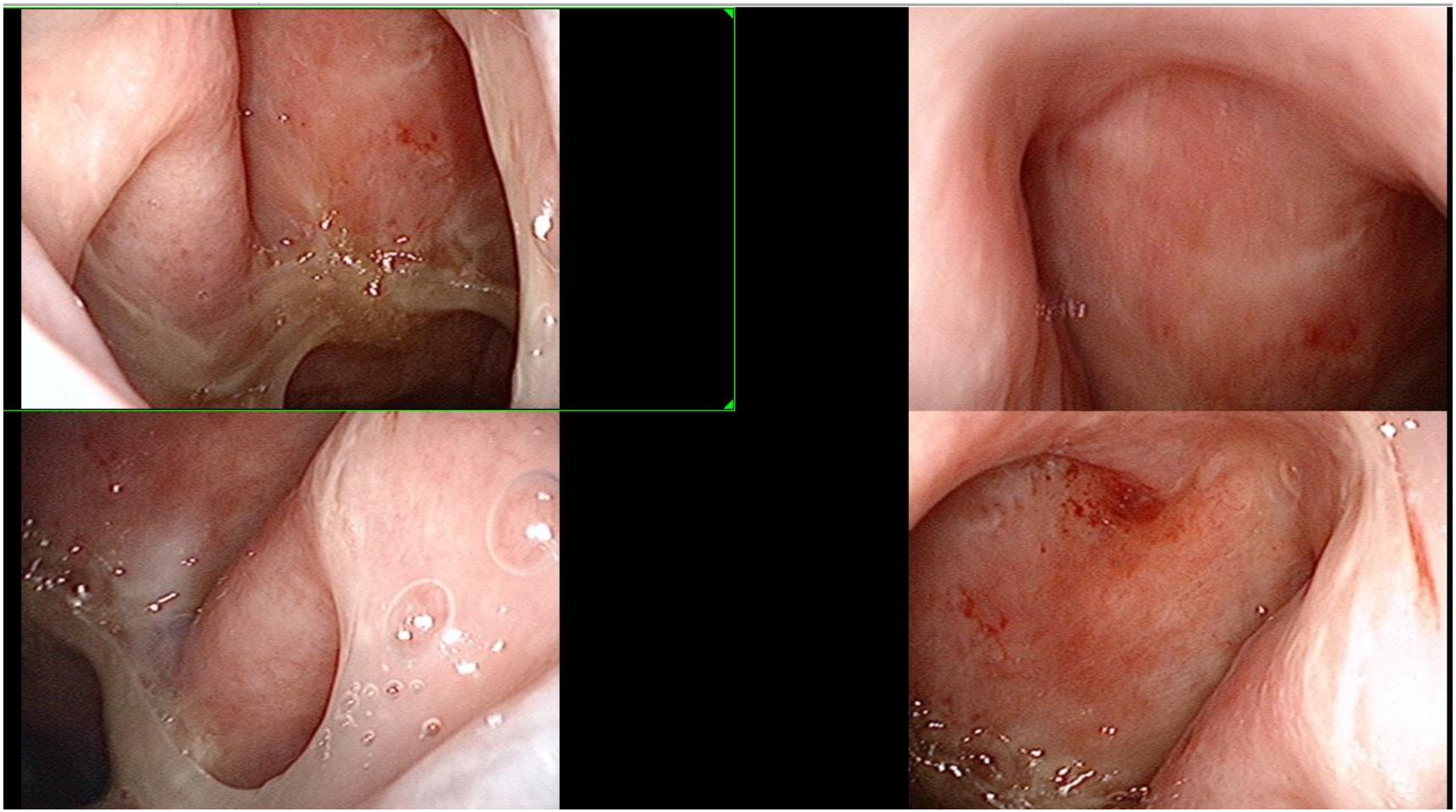
製作日期　2019年 9月 最後更新

Anatomy

- A cuboidal chamber slightly broader in the transverse dimension than in the anterior–posterior dimension.
- Anterior- nasal cavity; Inferior- oropharynx
- Roof- basilar portion of the sphenoid and occipital bones
- Floor- superior surface of the soft palate and nasopharyngeal isthmus.
- Lateral walls- contain pharyngotympanic tube (*Eustachian tube*) openings, bounded by a prominence known as the *torus tubarius* (formed by the cartilage of the E-tube), most common origin of NPC.
- Posterior to the torus is the pharyngeal recess, otherwise known as the fossa of Rosenmüller.
- Posterior wall - contains the superior pharyngeal constrictor muscle, pharyngobasilar fascia, and buccopharyngeal fascia.


Optic chiasm
Pituitary gland
Sphenoid sinus
Ethmoid sinus
Clivus
Nasal cavity
Nasopharynx
Hard palate
Anterior arch of atlas
Uvula
Epiglottis
Dens of C2 vertebra
A
B





Epidemiology and Etiology

- An uncommon cancer in most parts of the world.
- The age-adjusted incidence rate (per 100,000 people per year) among men ranges from 0.6 in the United States and Japan to 5.4 in Algeria, 5.8 in the Philippines, 11.0 in Singapore, 17.2 among Eskimos, Indians, and Aleuts in Alaska to 17.8 and 26.9 in Hong Kong and Guangdong Province in Southern China, respectively.
- A bimodal age distribution in low-risk populations.

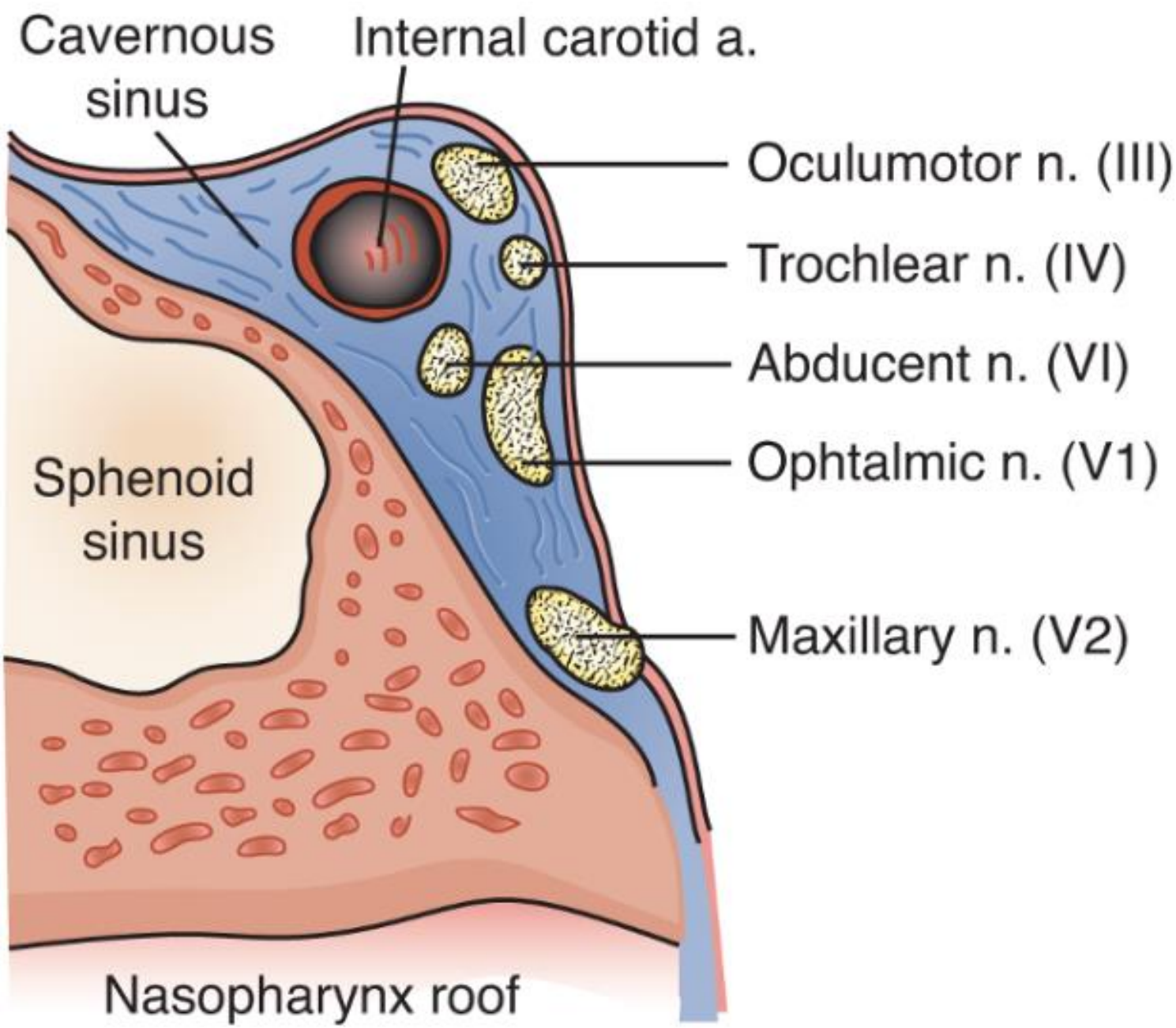
  1st peak incidence arises between 15 to 25 years of age; 2nd peak at 50 to 59 years of age.
- In high-risk populations, the peak incidence occurs in the fourth and fifth decades of life.
- Both genders have a similar age distribution; however, the male-to-female incidence ratio is 2:1 to 3:1.

- At least 3 important etiologic factors:
  (i) genetic, (ii) environmental, and (iii) viral.
- A genome-wide association study of NPC found three susceptibility loci and confirmed a linkage study that found a gene closely linked to the HLA locus conferred a greatly increased risk of this disease.
- Several HLA haplotypes, including A2, B46, and B17, are associated with an increased risk of developing NPC.

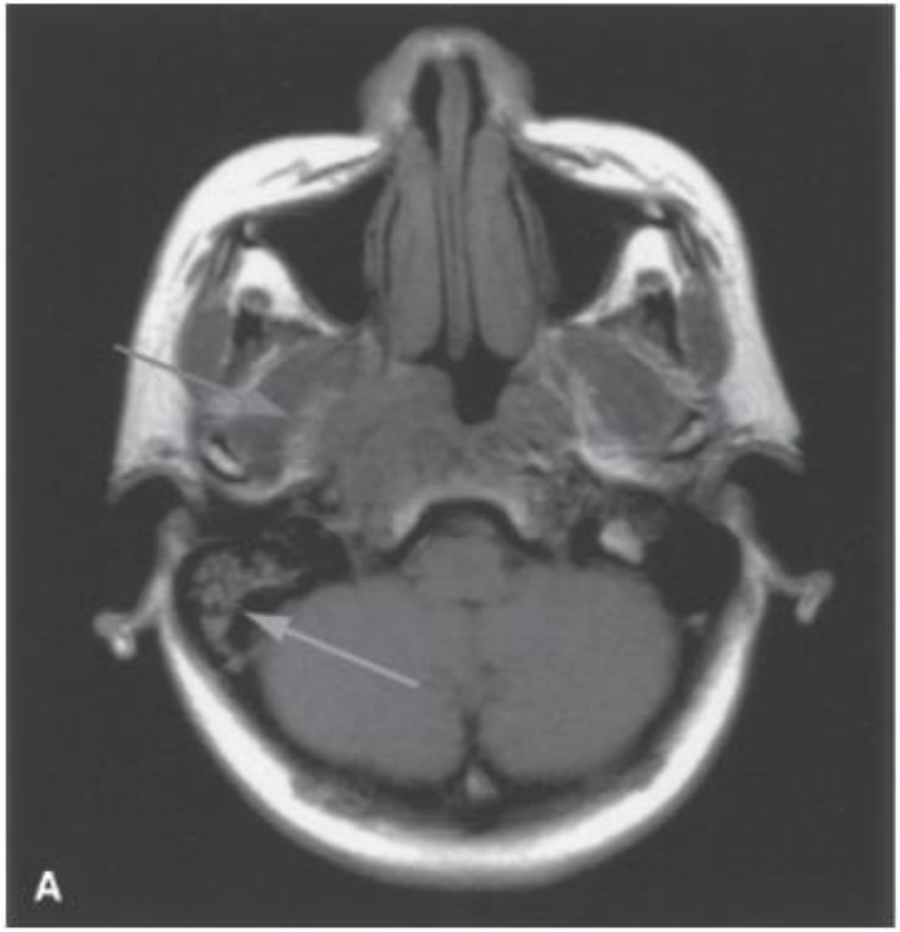
- Salted fish in Southern China has been implicated as an important environmental factor; Dimethylnitrosamine, a carcinogen found in salted fish, has been shown to induce carcinoma in the upper respiratory tract in rats.
- Other potential environmental etiologic factors- alcohol consumption and exposure to dust, fumes, formaldehyde, and cigarette

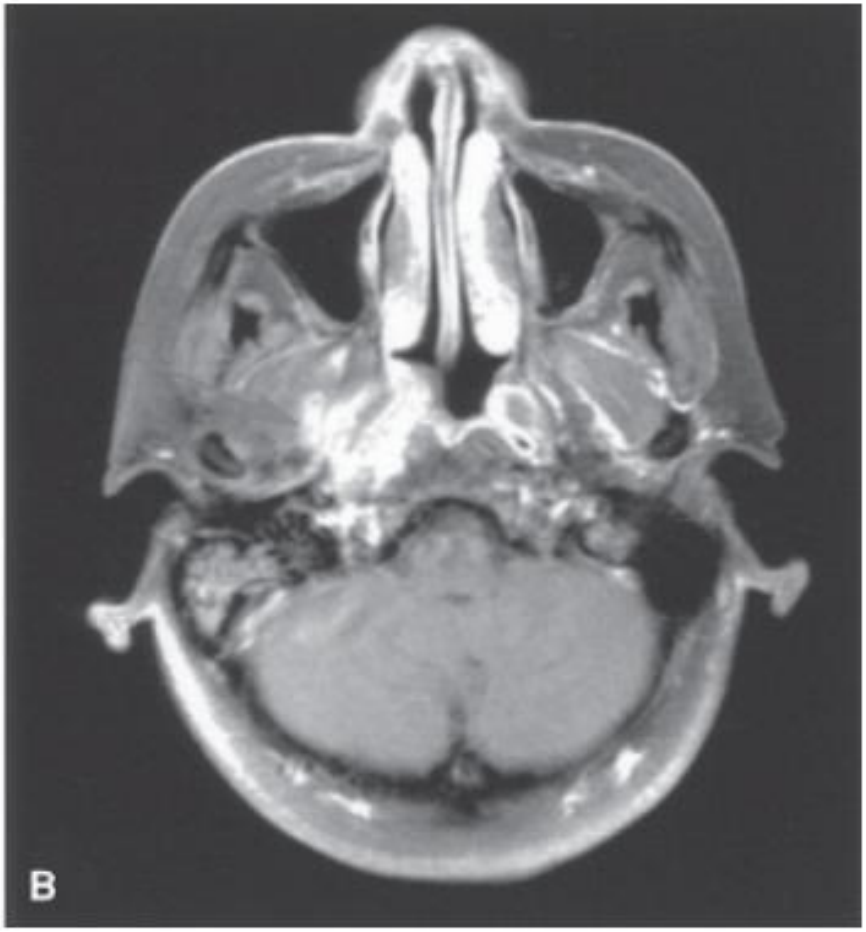
- Descendents from Chinese who have migrated from endemic areas to Western countries show progressively lower risk, but their incidence remains higher than that of the indigenous populations.
- American-born second-generation Chinese had a lower risk than the Asian-born first generation, while whites born in Southeast Asia had an increased risk compared to American-born whites.
- The incidence rate in Chinese who were natively born in China was 20.5, compared with 1.3 for Chinese and 0.2 for whites born in Canada.

- Epstein-Barr virus (EBV) has been associated with nasopharyngeal carcinoma, especially the nonkeratinizing type, irrespectively of ethnic or geographic origin.
- Premalignant lesions of nasopharyngeal epithelium show increased levels of EBV, suggesting that EBV infection may influence the early stages of tumorigenesis in NPC.

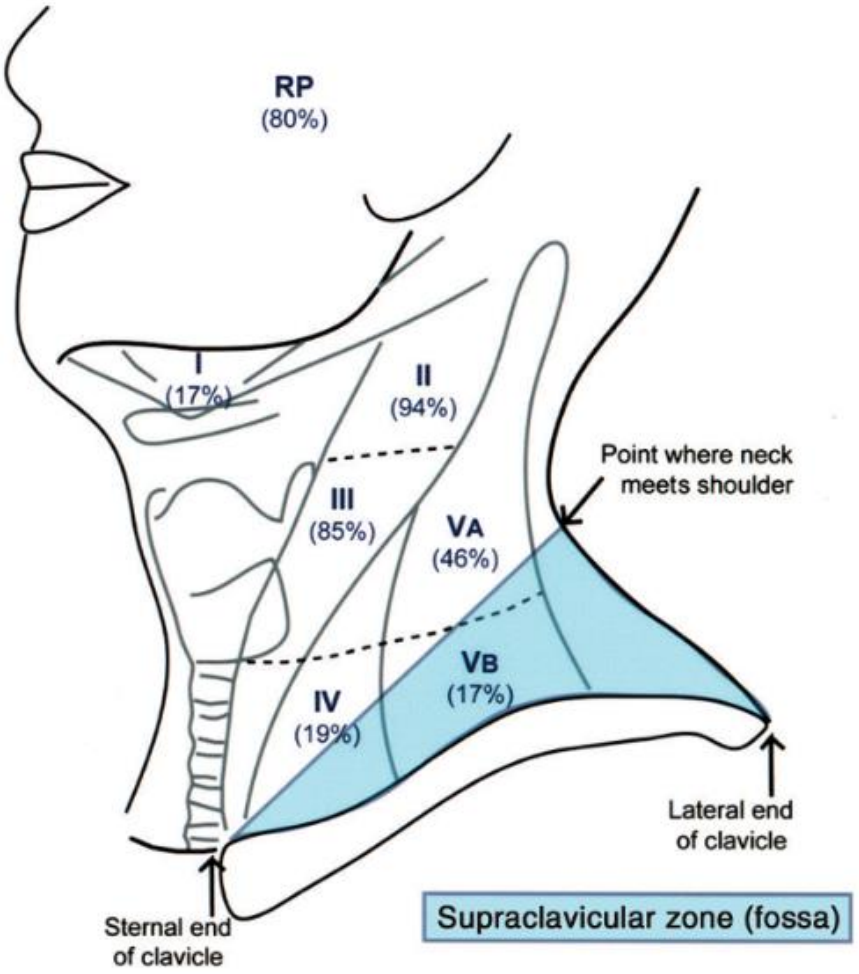

Cavernous sinus
Internal carotid a.
Oculumotor n. (III)
Trochlear n. (IV)
Abducent n. (VI)
Ophtalmic n. (V1)
Maxillary n. (V2)
Sphenoid sinus
Nasopharynx roof

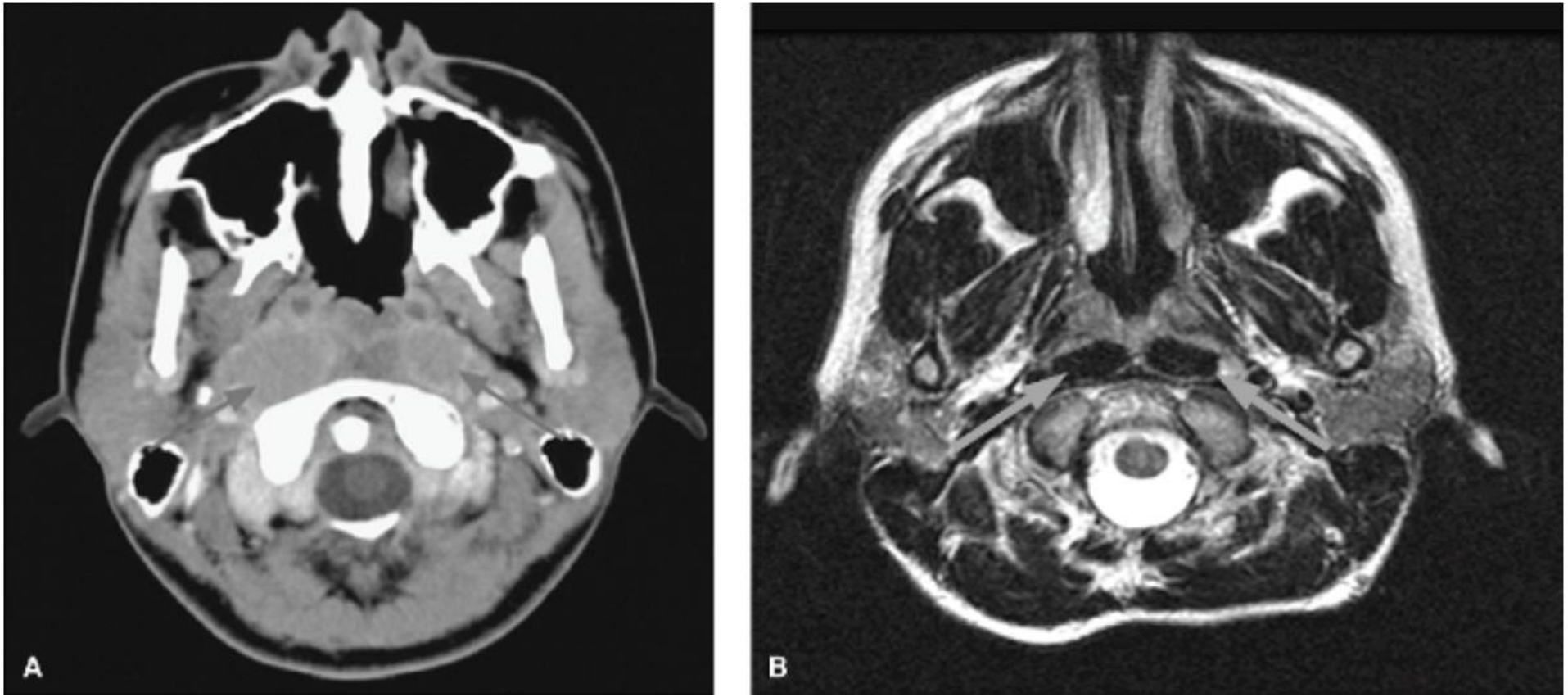
Parapharyngeal space invasion





- 85% to 90% of cases present with lymphatic spread to the ipsilateral nodes; bilateral spread is present in approximately 50% of cases.




A
B

Natural History- Hematogenous Dissemination

- Distant metastasis is present in 3% to 6% of the cases at presentation and may occur in 18% to 50% of cases during the disease course.
- The rate is highest in patients with advanced neck node metastasis, especially with low-neck involvement.
- Bone is the most common distant metastatic site, followed by the lungs and liver, with lung metastasis being associated with better prognosis than other sites.
- Brain and skin metastases rarely occur.

Clinical Presentation

- Three categories: (i) neck masses, usually appearing in the upper neck; (ii) presence of tumor mass in the NP (epistaxis, nasal obstruction and discharge); (iii) skull-base erosion and palsy of cranial nerves V and VI due to tumor extension superiorly (headache, diplopia, facial pain and numbness).

TABLE 41.4 INCIDENCE OF CRANIAL NERVE INVOLVEMENT BY NASOPHARYNGEAL CARCINOMA AT DIAGNOSIS

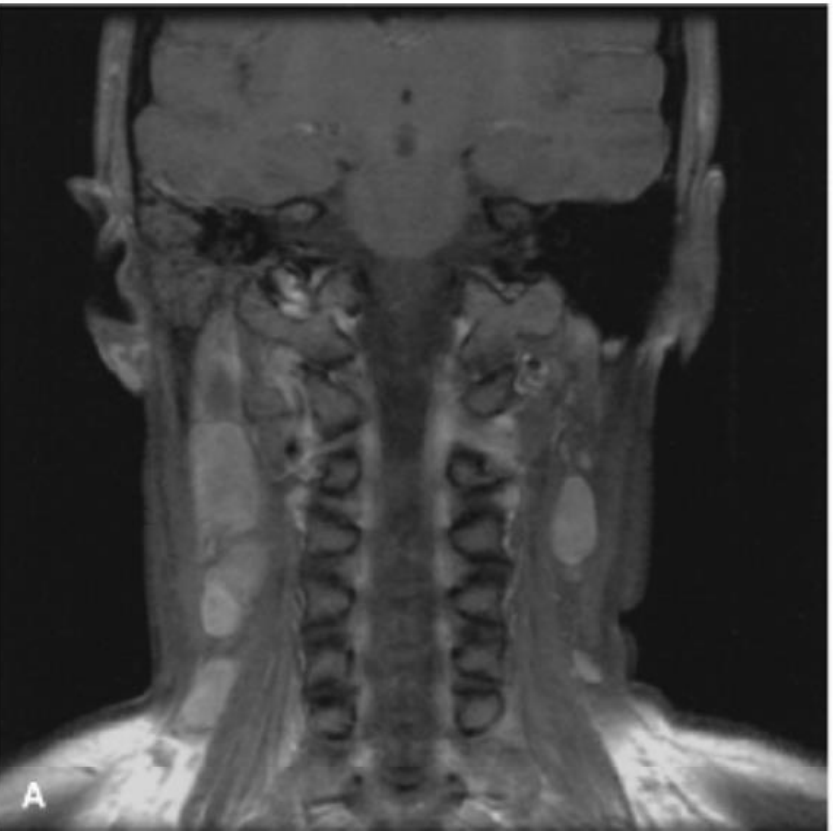
Cranial Nerve	*Chao and Perez*[355] *(n = 164) (%)*	*Chan et al.*[82] *(n = 722) (%)*
I	–	–
II	1.3	0.8
III	3.5	1.3
IV	2.4	0.6
V	7.8	V_1, 3.5; V_2, 5.8; V_3, 3.9
VI	13.3	5.1
VII	3.6	0.1
VIII	4.8	–
IX–XII	IX, 2; X, 5.4; XI, 1.3; XII, 4.8	2.4

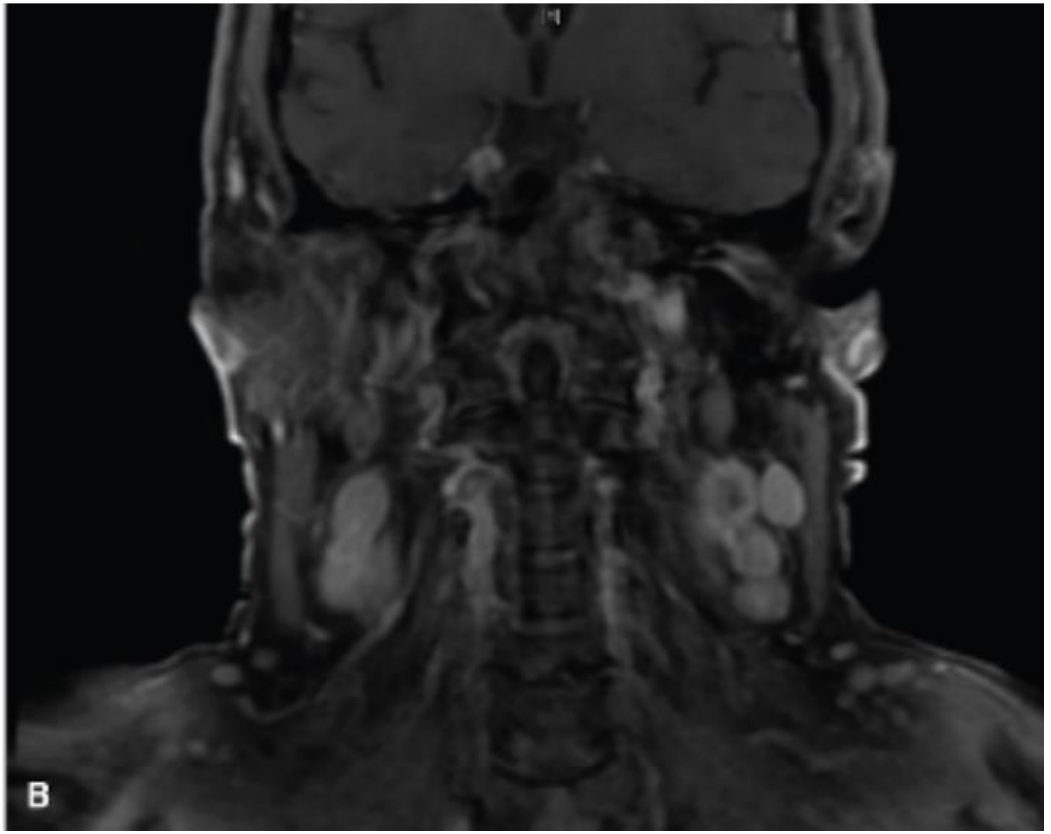
Diagnostic and Staging Workup

- Biopsy of the primary tumor.
- For suspicious cases of a nasopharyngeal primary tumor with lack of visible tumor, random biopsies of the most commonly involved sites are warranted: pharyngeal recess on each of the lateral walls and superior posterior wall of the nasopharynx.
- FNA of a suspicious neck mass may establish the presence of metastatic nasopharyngeal carcinoma in the regional lymphatics; performed prior to the biopsy of the NP when the primary tumor is not clinically detectable.

- CT and MRI of the head and neck are useful in the evaluation of tumor erosion into the bony structures of the base of skull along with retropharyngeal and cervical lymphadenopathy.
- MRI is the preferred imaging technique in the staging evaluation
- MRI may be necessary for proper staging because CT has limitations in accurately defining tumor extension into these regions.
- MRI is superior to CT in delineating muscle, soft tissue involvement, and examination of the skull base.

- According to a study by Van den Brekel et al., 53 lymph node metastases are commonly recommended to be radiologically defined by presence of central necrosis, extracapsular spread, shortest axial diameter ≥10 mm (11 mm for the juglodigastric node and 5 mm for the retropharyngeal node), or a cluster of three or more LNs that are borderline in size.
- Detailed evaluation of nodal enlargement by palpation and imaging should consist of the size and location of the node, unilateral/bilateral involvement, and assessment of SCF involvement.


A


B

Staging System

- The AJCC, International Union Against Cancer (UICC), and Ho staging systems are the most commonly used systems in the English-language literature.
- One advantage of the Ho system is its approach to N-stage classification, which uses level or location of nodal involvement.

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
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

Definition of Regional Lymph Node (N)

N Category	N Criteria
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

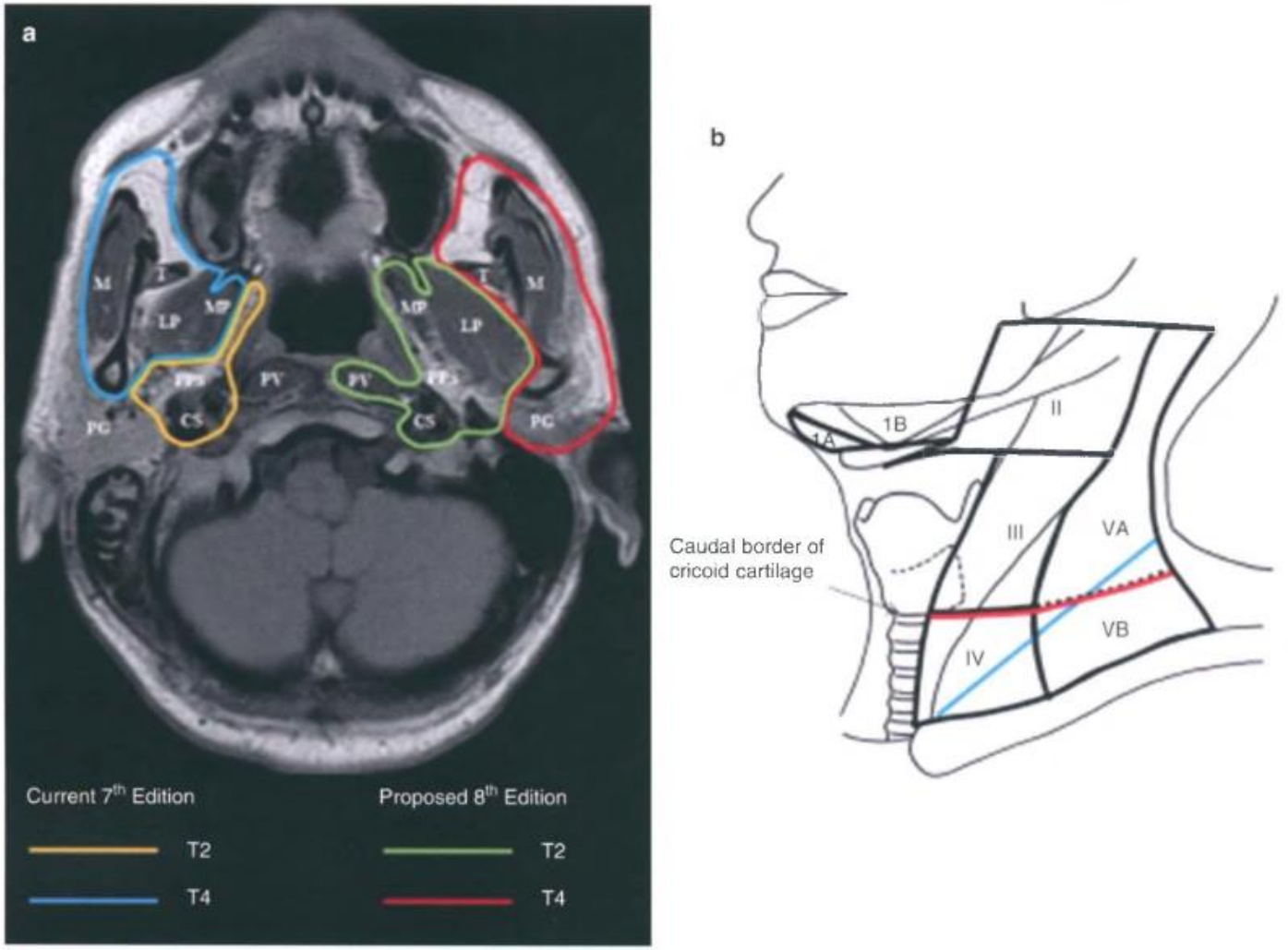


Fig. 9.2 Differences in defining criteria between the 7th Edition and the 8th Edition for staging of NPC: (**a**) changing the extent of soft tissue involvement as T2 and T4 criteria. Abbreviation: CS = carotid space, LP = lateral pterygoid muscle, M = masseter muscle, MP = medial pterygoid muscle, PG = parotid gland, PPS = parapharyngeal space, PV = prevertebral muscle, T = temporalis muscle, (**b**) replacing supraclavicular fossa (*blue*) by lower neck, i.e., below caudal border of cricoid cartilage (*red*) as N3 criteria. From Pan et al.,[27] with permission

Pathologic Classification

- The vast majority of malignant nasopharyngeal tumors are carcinoma (80% to 99%), with the remainder of these lesions (about 5%) being lymphomas.
- Rare malignant tumors- adenocarcinoma, plasmacytoma, melanoma, and sarcomas.
- WHO pathologic classification in 2005, includes three major types.
- Keratinizing squamous cell carcinoma is distinguished by the presence of keratin pearls or intracellular keratin.
- Nonkeratinizing carcinoma is characterized by the complete absence of keratin formation and is further subdivided into differentiated and undifferentiated subtypes; strong association with EBV positivity
- Basaloid squamous cell carcinoma- composed of closely packed small tumor cells that form a lobular and, at times, pallisading pattern along with focal squamous carcinoma elements; quite rare, with a frequency of <0.2%.
- The keratinizing type may have a correlation with HPV.

TABLE 41.7 FREQUENCY OF DIFFERENT HISTOLOGIC SUBTYPES OF NASOPHARYNGEAL CARCINOMA

	High-Incidence Population: Hong Kong (%)	*Intermediate-Incidence Population: Tunisia (%)*	*Low-Incidence Population: United States (%)*
Keratinizing squamous cell carcinoma	1	8	25
Nonkeratinizing carcinoma	99	92	75
Undifferentiated	92	76	NA
Differentiated	7	16	NA
Basaloid-squamous carcinoma	<0.2	NA	NA

NA, not available.

Modified from Chan J, Bray F, McCarron P, et al. Nasopharyngeal carcinoma. In: *Pathology and genetics of head and neck tumours.* Lyon, France: IARC Press; 2005:85–97.

Prognostic Factors

- The extent of local invasion, regional lymphatic spread, and distant metastasis, as reflected by the TNM staging, is the most important prognostic factor.
- Advanced T-category is associated with worse local control and overall survival; advanced N-category predicts increased risk of distant metastasis and worse survival.
- Presence of distant metastasis (M1) upon presentation usually indicates poor prognosis, and treatment has conventionally been palliative in nature.

Gender and Age

- Most series found significantly better prognosis for females and younger patients.
- In 759 patients, Sham and Choy showed a higher 5-year survival rate in females compared with males (45% vs. 28%) and in patients younger than 40 vs. older than 40 years of age (50% vs. 40%, $p = .002$); but age not significantly affect the 10-year survival rate.
- Multivariate analysis of 1,294 patients by Au et al. also showed worse cancer-specific death rates in males (hazard ratio [HR] = 1.28, $p = .02$) and patients older than 50 years (HR = 1.79, $p < 0.001$).

Histology

- Although not all studies found histology to be an independent prognostic factor, many found nonkeratinizing and undifferentiated carcinomas (formerly known as lymphoepitheliomas) to be more radiosensitive and offer better prognosis than keratinizing squamous cell carcinoma.
- Regarding ethnicity as a prognostic factor, a study by Corry et al. showed no prognostic difference between ethnic Asian and non-Asian patients with nonkeratinizing carcinoma.

EBV and Other Biomarkers

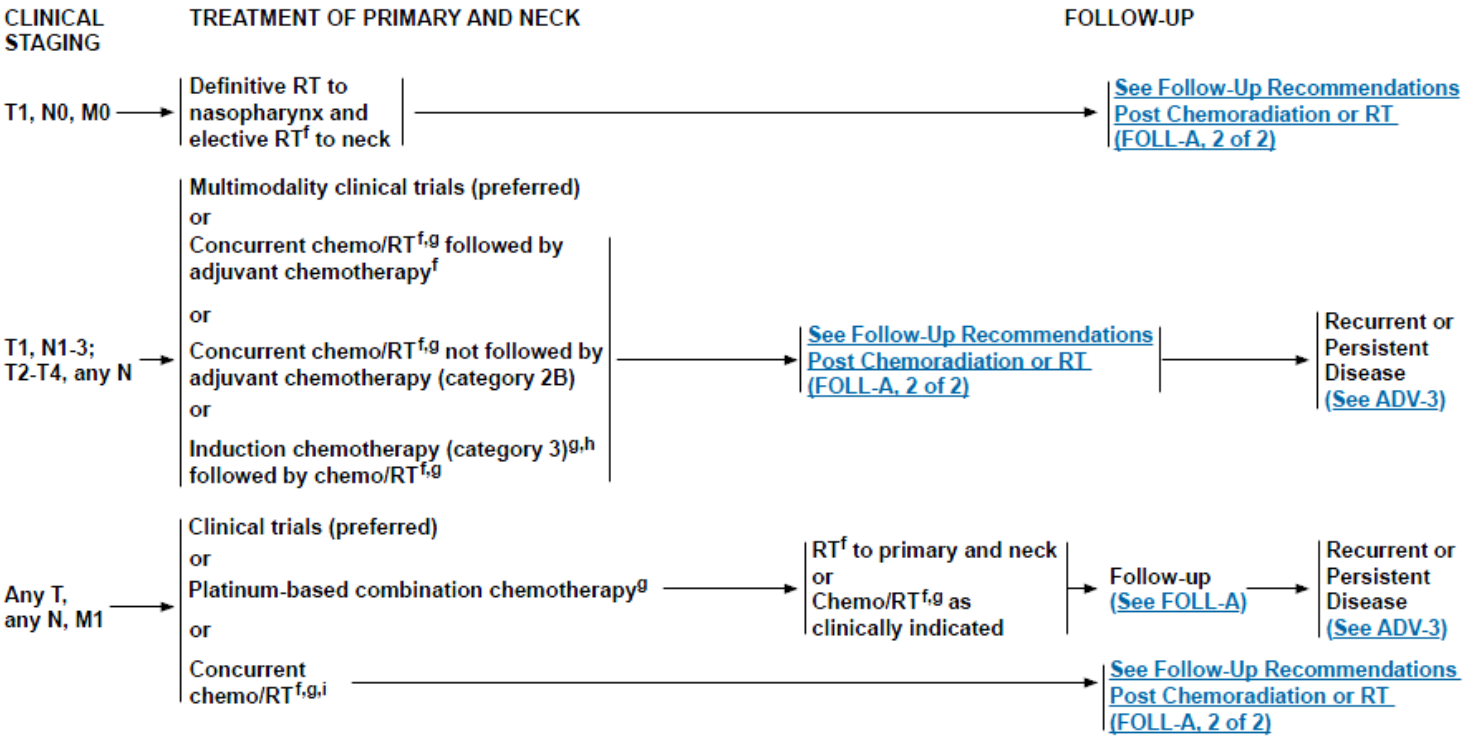
- While some studies showed that elevated level of serum anti-EBV antibodies could indicate presence of disease, others showed anti-EBV antibody titers to have little value for posttreatment surveillance.
- The prognostic value of such titers prior to treatment has also been controversial.
- While Xu et al. found that high EBV DNase-specific neutralizing antibody at diagnosis predicted significantly worse event-free and overall survival, others found that a number of antibodies (VCA-IgG, VCA-IgA, EA-IgG, EA-IgA, EBNA-IgG, EBNA-IgA) could not predict prognosis.

Treatment strategy

- Because of the anatomic location—proximity to critical structures—surgical exposure and tumor resection with sufficient margins have been very challenging.
- Primary surgical intervention was rare after the 1950s for these reasons, with surgical interventions employed mainly for biopsy to gain histologic confirmation and salvage therapy for persistent or recurrent cancer.
- Primary treatment since has typically employed RT alone and, more recently, in combination with chemotherapy.

NCCN Guidelines Version 2.2017
Cancer of the Nasopharynx

NCCN Guidelines Index
Table of Contents
Discussion

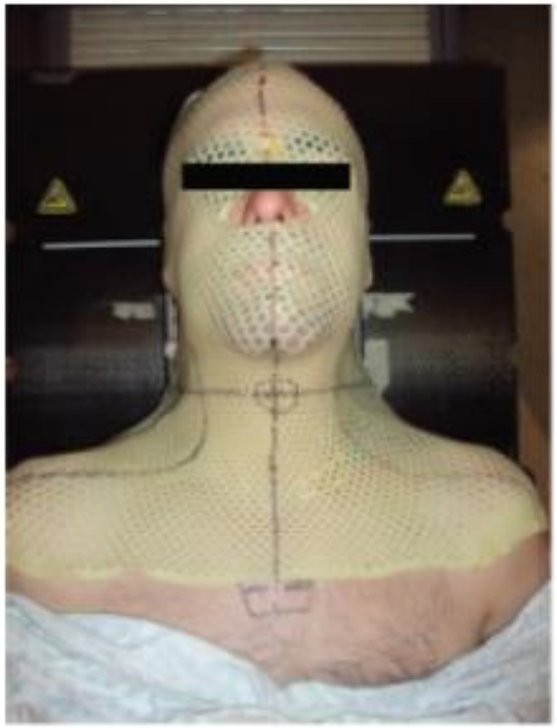


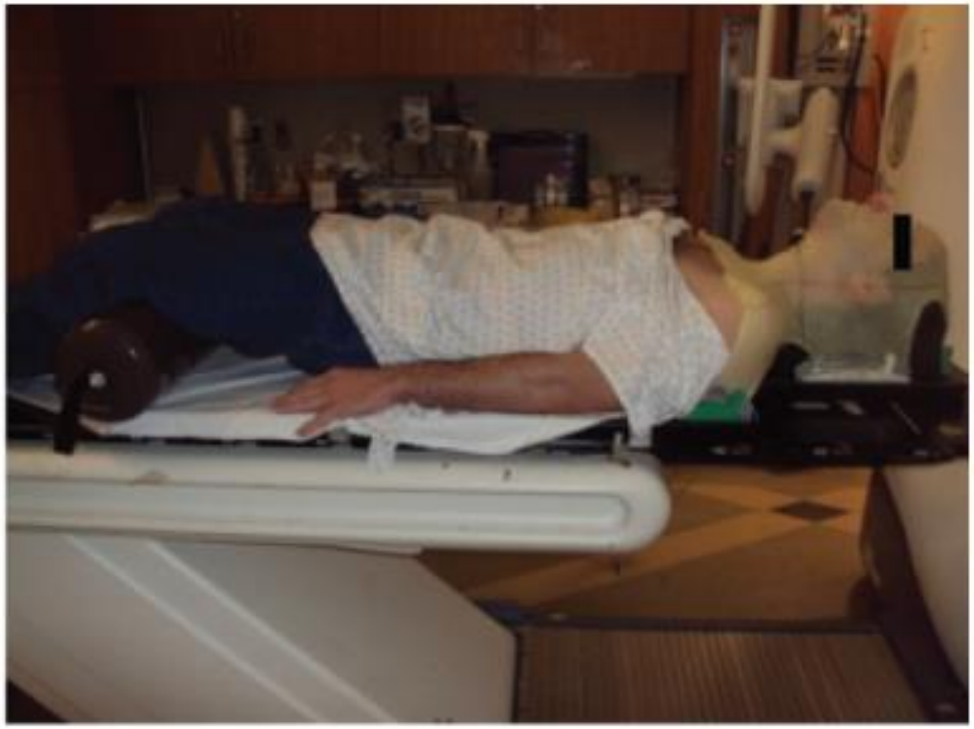
[f] See Principles of Radiation Therapy (NASO-A).
[g] See Principles of Systemic Therapy (CHEM-A).
[h] See Discussion on induction chemotherapy.
[i] Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any nodal site.
[j] See Principles of Surgery (SURG-A).

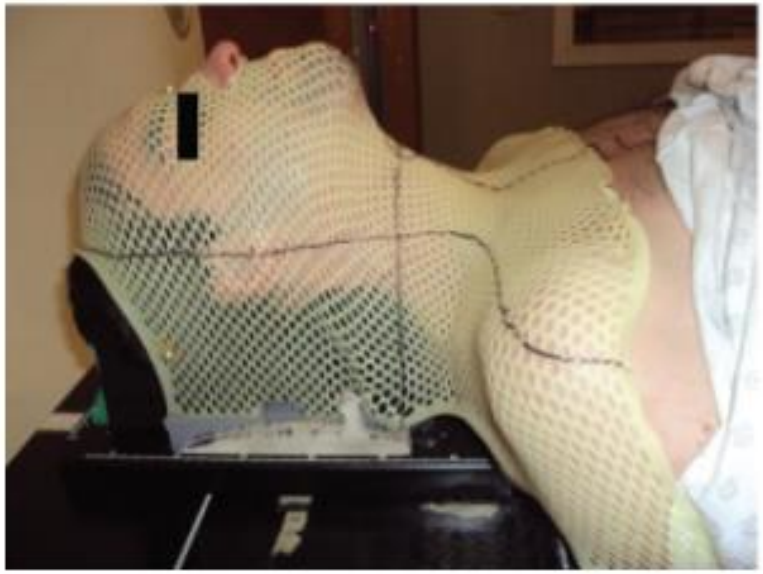
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

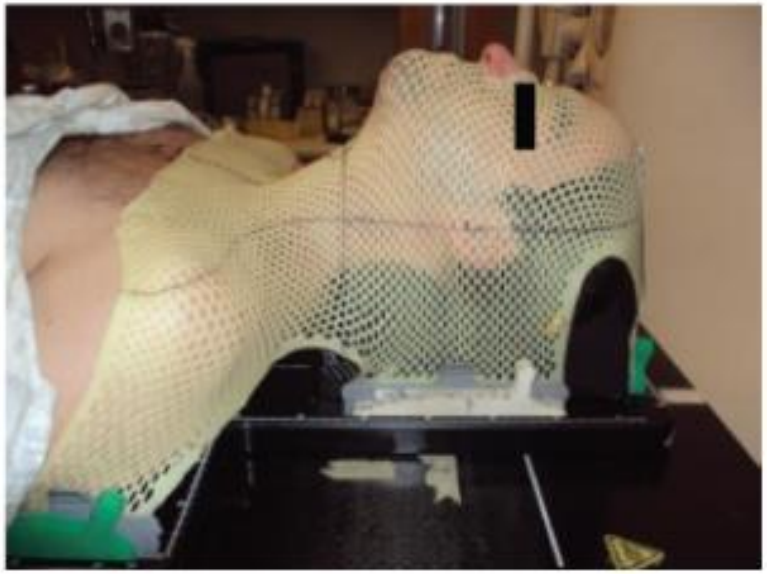
Radiation Therapy

- For planning, the patient should be set up in a supine position with head extended for adequate separation between the primary tumor/retropharyngeal nodes and the upper neck nodes.
- The tip of the uvula and the base of the occiput should be on a parallel plane to the beam axis.
- The patient is immobilized with a thermoplastic mask covering the head-to-shoulder region
- For patients to be treated by conventional 2D technique, a mouth bite is useful to minimize the dose to the oral cavity, with enlarged neck nodes to be marked with wire before imaging.

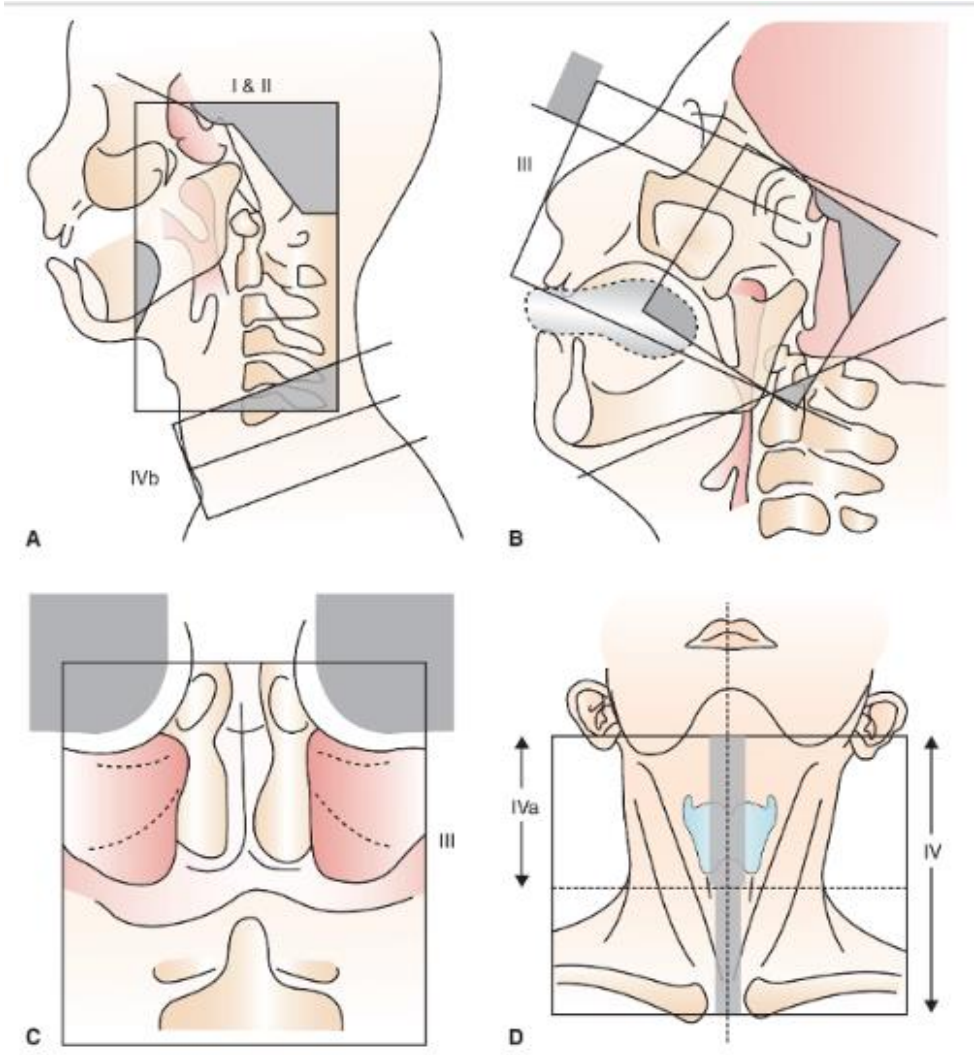








Conventional 2D Treatment Techniques



Dose, Time, and Fractionation

- A significant dose–response relation was observed in the majority of retrospective studies, based on patients irradiated with 2D techniques.
- Marks et al. and Vikram et al.showed that local control was significantly improved in patients who received >67 Gy to the tumor target.
- Perez et al. observed that patients with T1-2 tumors had a local tumor control rate of 100% for those given >70 Gy, compared with 80% for those treated with 66 to 70 Gy.
- Local control for patients with T3-4 tumors remained <55%, even with total dose >70 Gy.
- Besides consideration of the prescribed dose, the problem of sufficient coverage has to be overcome for advanced tumors.

IMRT Techniques

- Superior target volume coverage; limit the dose to surrounding normal tissues.
- Possibility of biologic enhancement by simultaneous modulated accelerated-radiation therapy (SMART), (dose painting), as a new way of delivering an accelerated fractionation (AF) schedule.

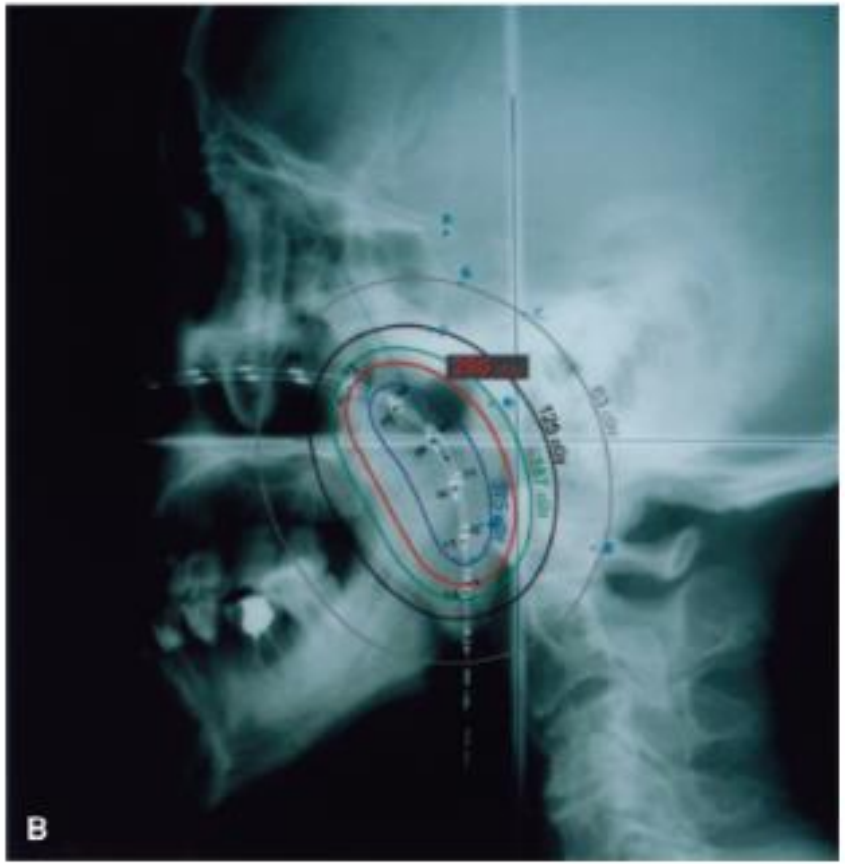
TABLE 41.10 INTENSITY-MODULATED RADIATION THERAPY FOR NASOPHARYNGEAL CARCINOMA: AN EXAMPLE OF NORMAL TISSUE DOSE CONSTRAINTS[a]

Structure	*Constraint*
Critical Structures	
Brainstem	Maximum <5 Gy or 1% of PTV cannot exceed 60 Gy
Optic nerves	Maximum <54 Gy or 1% of PTV cannot exceed 60 Gy
Optic chiasm	Maximum <54 Gy or 1% of PTV cannot exceed 60 Gy
Spinal cord	Maximum <45 Gy or 1 cc of the PTV cannot exceed 50 Gy
Mandible and temporomandibular joint	Maximum <70 Gy or 1 cc of the PTV cannot exceed 75 Gy
Brachial plexus	Maximum <66 Gy
Temporal lobes	Maximum <60 Gy or 1% of PTV cannot exceed 65 Gy
Other Normal Structures	
Oral cavity	Mean <40 Gy
Parotid gland	Mean ≤26 Gy (should be achieved in at least one gland) or at least 20 cc of the combined volume of both parotid glands will receive <20 Gy or at least 50% of the gland will receive <30 Gy (should be achieved in at least one gland)
Cochlea	V_{55} <5%
Eyes	Mean <35 Gy, Max <50 Gy
Lens	Max <25 Gy
Glottic larynx	Mean <45 Gy
Esophagus, postcricoid pharynx	Mean <45 Gy

Brachytherapy

- Intracavitary insertions or interstitial implants have been used in T1 to T3 NPC as a boost treatment following EBRT or in the treatment of recurrent disease, either alone or in combination with EBRT.
- Not suitable for tumors with intracranial extension because of the rapid reduction of dose as distance from the radioactive source increases.
- Since the advent of IMRT as primary RT for NPC and with its demonstration of excellent local control, the use of brachytherapy as a boost treatment following definitive IMRT has dramatically declined.
- In the past, intracavitary brachytherapy was delivered using LDR techniques.
- At present, remote afterloading, fractionated HDR techniques are more commonly used

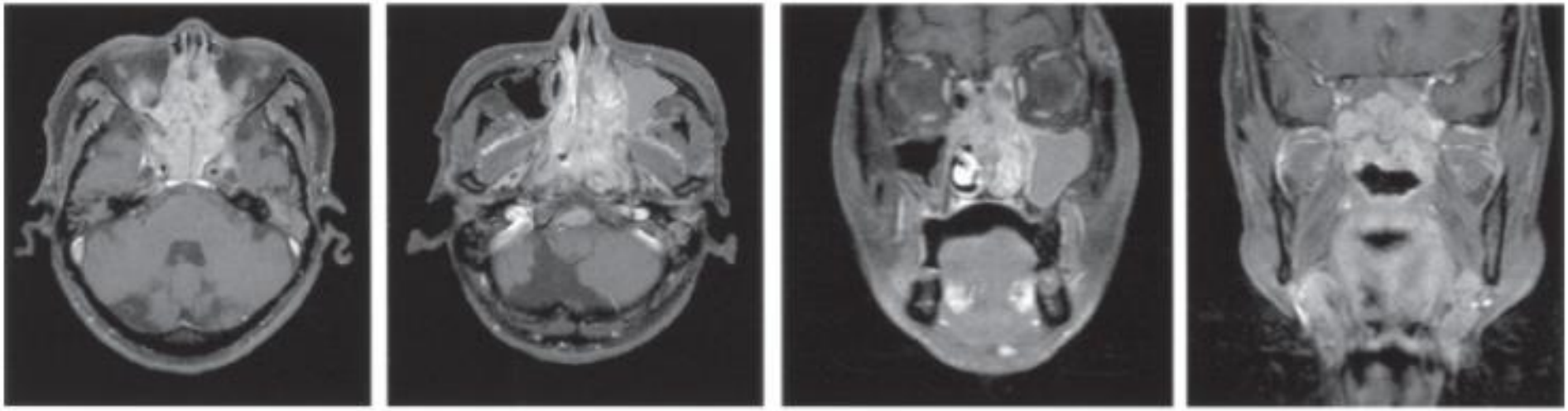

A


B

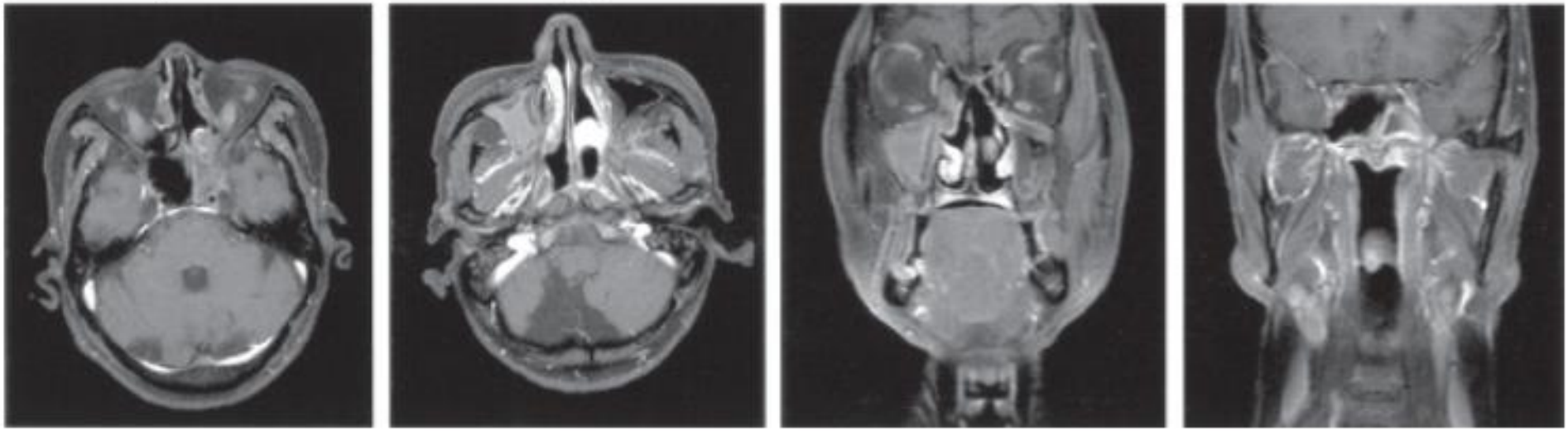
Neoadjuvant Chemotherapy

- The effect of adding neoadjuvant chemotherapy to CCRT is a topic of much current interest and the subject of two ongoing phase III randomized trials.
- Multiple phase II trials have shown excellent outcomes and tolerability with a variety of regimens.
- One recent randomized phase II trial demonstrated an overall survival benefit for docetaxel/CDDP followed by CDDP-RT when compared to concurrent CDDP-RT alone.
- Although the difference in 3-year progression-free survival did not reach statistical significance (88.2% vs. 59.2%, *p* = .12), 3-year overall survival was significantly improved in the neoadjuvant arm (94.1% v 67.7%, *p* = .012).

Pretreatment



After 3 cycles of induction chemotherapy



- Five-year survival rates ranged from 36% to 58%

TABLE 41.18 OVERALL SURVIVAL AFTER CONVENTIONAL RADIOTHERAPY

Author	Year	Patients (n)	5-Year Survival Rate (%)	Analysis
Hoppe[32]	1976	82	57	Actuarial
Mesic[146]	1981	251	52	Actuarial disease-free
Chu[31]	1984	80	36	Actuarial
Vikram[145]	1985	107	56	Actuarial[a]
Wang[302]	1990	185	43	Absolute
Bailet[301]	1992	103	58	Actuarial

[a]Estimated from survival curve.

TABLE 41.20 RESULTS FROM CONTEMPORARY IMRT SERIES WITH OR WITHOUT CHEMOTHERAPY

Study	Year	Stage	Number	Median Follow-up (Months)	Time Point (Years)	Local Control Rate (%)	Regional Control Rate (%)	Distant-Metastasis–Free Rate (%)	OS (%)
Lee et al.[166] (UCSF)	2002	All	67	31	4	97	98	66	88
Kwong et al.[70] (Hong Kong)	2004	T1 N0-1[a]	33	24	3	100	92	100	100
Kam[171] (Hong Kong)	2004	All	63	29	3	92	98	79	90
Wolden et al.[193] (MSKCC)	2006	All	74	35	3	91	93	78	83
Kwong et al.[78] (Hong Kong)	2006	III-IVB[a]	50	25	2	96	NA	94	92
Lee et al.[305] (MSKCC)	2009	All	68	31	2	93	91	85	80
Tham et al.[307] (Singapore)	2009	All	195	37	3	90	NA	89	94
Lin et al.[306] (China)	2009	II-IV[a]	323	30	3	95	98	90	90
Wong et al.[357] (China)	2010	All	175	34	3	94	93	87	87
Lin et al.[309] (China)	2010	IIB-IVB[a]	370	31	3	95	97	86	89
Kam et al.[308] (Hong Kong)	2010	All	231	59	6	82	91	75	66
Ng et al.[311] (Hong Kong)	2011	All	193	30	2	95	96	90	92
Xiao et al.[310] (China)	2011	III-IVA[a]	81	54	5	95	NA	NA	75
Bakst et al[150] (MSKCC)	2011	II-IVB[a]	25	33	3	91	91	91	89
Xiayun et al.[313] (China)	2011	IIB-IVB[b]	54	30	3	95	98	86	88
Ma et al.[231] (Hong Kong)	2011	III-IVB[b]	30	32	2	93	93	93	90
Lee et al.[232] (MSKCC)	2011	IIB-IVB[c]	42	30	2	NA	NA	91	91
Su et al.[312] (China)	2012	I-IIB[b]	198	51	5	97	98	98	NA

Reference

- Perez CA and Brady LW: Principles and Practice of Radiation Oncology, 7th ed. Lippincott Williams & Wilkins, 2018.
- DeVita VT, Lawerence TS, et al: Cancer: Principles and practice of Oncology. 10th ed. Lippincott Williams & Wilkins, 2015.
- 本院癌症臨床治療小組治療準則
- NCCN guidelines (http://www.nccn.org)
- 8th AJCC staging