Chapter 5
Nasopharyngeal Cancer

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PEARLS

- Epidemiology
  - Rare in the USA (<1 in 100,000) but endemic in SE Asia (25–50 in 100,000)
  - #1 most common HN cancer and #6 in cancer deaths in SE Asia
  - Two peak ages: 15–25 and 50–60; males > females (2:1)
- Histology
  - WHO I: Keratinizing; tobacco-associated; poor LRC
  - WHO IIA/IIB: Non-keratinizing/undifferentiated; endemic, EBV-associated; high DM
  - Lymphoepithelioma = with high lymphoid component; better LRC but same OS due to increased DM
  - Other nasopharynx tumors: lymphoma, minor salivary gland, plasmacytoma, melanoma, chordoma, rhabdomyosarcoma

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Table 5.1 ANATOMY

Border	Structure(s)	Pattern of spread	Significance
Lateral	Eustachian tube, torus tubarius, fossa of Rosenmuller, superior pharyngeal constrictors, medial pterygoid plate	Parapharyngeal space	Fossa of Rosenmuller is the most common site for NPC. Retroparotid space syndrome = involvement of CN IX–XII and cervical sympathetics
		Masticator space	Trismus
Anterior	Posterior nasal septum/choanae	Pterygopalatine fossa (PPF) via sphenopalatine foramen from nasal cavity	Tumors can extend proximally along V2 from PPF to cavernous sinus
Posterior	Clivus and C1–2	Retropharyngeal (RP) nodes and prevertebral space	>75% of patients are cN+, 90% have subclinical nodes, and 40–50% have bilateral nodes. Level 2 and lateral RP nodes are the first echelon
Superior	Sphenoid bone/ sinus	Skull base	Foramen ovale (CN V3) and foramen lacerum commonly involved. True intracranial extension is uncommon (<10%). Petrosphenoidal syndrome = extension through foramen lacerum to cavernous sinus
Inferior	Roof of soft palate	Hard palate (oropharynx)	Infrequent compared to anterior, superior, or lateral spread

WORKUP

- *H&P*. Common signs/symptoms include hearing loss, otitis media, neck mass, nasal obstruction, epistaxis, headache, diplopia, and trismus. Perform fiberoptic nasopharyngolaryngoscopy and thorough oropharyngeal and neck exam. Also perform otoscopy. Thorough CN exam is critical.
- Labs: CBC, LFTs, BUN/Cr, baseline TSH, EBV IgA/DNA titer.

- MRI ± CT head/neck with contrast. CT optimally demonstrates cortical bone and MRI, medullary bone. A normal-appearing basisphenoid (clivus) on CT may demonstrate marked tumor infiltration on MRI.
- For Stage III/IV, consider CT of chest and abdomen + bone scan or PET/CT scan.
- Pre-RT dental, nutritional, speech and swallow, and audiology evaluations.

STAGING: NASOPHARYNGEAL CANCER

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2010 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

Table 5.2 (AJCC 7TH ED., 2010)

Primary tumor (T)	
TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
Tis:	Carcinoma in situ
T1:	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2:	Tumor with parapharyngeal extension*
T3:	Tumor involves bony structures of skull base and/or paranasal sinuses
T4:	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, and orbit or with extension to the infratemporal fossa/masticator space

**Note*: Parapharyngeal extension denotes posterolateral infiltration of tumor

Regional lymph nodes (N)	
NX:	No regional lymph node metastasis can be assessed
N0:	No regional lymph node metastasis
N1:	Unilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension*
N2:	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*

continued

Table 5.2 (continued)

N3:	Metastasis in a lymph node(s)** >6 cm and/or to supraclavicular fossa*
N3a:	Greater than 6 cm in dimension
N3b:	Extension to the supraclavicular fossa*

**Note*: Midline nodes are considered ipsilateral nodes
***Note*: Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, and (3) the point where the neck meets the shoulder (Fig. 4.2). Note that this would include caudal portions of levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b

Distant metastasis (M)	
MX:	Distant metastasis cannot be assessed
M0:	No distant metastasis
Stage grouping	
0:	TisN0M0
I :	T1N0M0
II:	T1N0M0, T2N0-1M0
III:	T1-2N2M0, T3N0-2M0
IVA:	T4N0-2M0
IVB:	Any T, N3, M0
IVC:	Any T, any N, M1

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media

Table 5.3 (AJCC 8TH ED., 2017)

Definitions of AJCC TNM	
Definition of Primary Tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No tumor identified but there is EBV-positive cervical node involvement
T1	Tumor confined to the nasopharynx or extension to the 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 the skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension; involvement of cranial nerves, hypopharynx, orbit, and 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 the cervical lymph node(s) and/or unilateral or bilateral metastasis in the retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of the cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in the greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in the greatest dimension, and/or extension below the caudal border of cricoid cartilage

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	Stage 0
T1	N0	M0	Stage I
T1, T0	N1	M0	Stage II
T2	N0	M0	Stage II
T2	N1	M0	Stage II
T1, T0	N2	M0	Stage III
T2	N2	M0	Stage III
T3	N0	M0	Stage III
T3	N1	M0	Stage III
T3	N2	M0	Stage III
T4	N0	M0	Stage IVA
T4	N1	M0	Stage IVA
T4	N2	M0	Stage IVA
Any T	N3	M0	Stage IVA
Any T	Any N	M1	Stage IVB

TREATMENT RECOMMENDATIONS

Table 5.4 TREATMENT RECOMMENDATIONS

2010 AJCC stage	Recommended treatment
Stage I	RT alone (70/2 Gy)
Stages II–IVB	Concurrent chemo-RT followed by adjuvant chemo 70/2 Gy + cisplatin 100 mg/m^2 on days 1, 21, and 42 → cisplatin/5-FU × 3c Neck dissection for persistent/recurrent neck nodes IMRT may improve LRC and reduces severe xerostomia 80% → 35–40% Neoadjuvant chemo (platinum/5FU +/− taxane) is under investigation
Stage IVC	Platinum-based combination chemo; if CR, definitive RT, otherwise palliative RT dose to metastatic sites
Local recurrence	Re-irradiation with IMRT, SRS, or brachytherapy. Cumulative dose is limited with respect to surrounding normal tissue tolerance. Alternative, surgery
Pediatric	Per COG ARAR 0331 protocol: Stage I: RT alone (61.2/1.8 Gy for Stage I; 66.6/1.8 Gy for Stage IIa) with daily amifostine Stage ≥ II: Cisplatin/5-FU × 3c → RT (CR/PR to chemo 61.2/1.8 Gy, SD to chemo 70.2/1.8 Gy) with daily amifostine and concurrent cisplatin ×3c 36–46/2–3 Gy to unresectable metastases

STUDIES

RT ± CHEMOTHERAPY

- *Int 0099* (Al Sarraf JCO 1998). 147 patients with Stage III–IV disease randomized to RT (2/70 Gy) vs. chemo-RT (2/70 Gy + concurrent cisplatin (100 mg/m^2) × 3 → adjuvant cisplatin/5-FU × 3 cycles). Used old staging, so many Stage II would now be included. Chemo-RT improved 3-year OS (47 → 78%) and PFS (24 → 69%). Trial stopped early due to OS benefit. Criticized because of poor LRC and OS for RT alone group and high % of WHO I tumors (rare outside the USA).
- Wee (JCO 2005). Confirmed Int 0099 results with 221 patients from Singapore with Stage III–IV disease and same randomization. Chemo-RT improved 2-year OS (78 → 85%), DFS (57 → 75%) and DM (30 → 13%).

- Chan (IJROBP & JNCI 2005a, b). Phase III study showing benefit of weekly, low-dose (40 mg/m^2) cisplatin with RT vs. RT alone in 350 patients. No adjuvant chemotherapy. Cisplatin-RT improved 5-year OS (59 → 70%) with main benefits seen in T3/T4. Relatively low toxicity compared to Int 0099 chemo.
- MAC-NPC meta-analysis (Blanchard, Lancet Oncol 2015). 19 trials with 4806 pts. 5-yr OS benefit for concurrent and adjuvant chemo (12.4%) or concurrent chemo alone (9.4%), but not adjuvant chemo alone or induction chemo alone. Concurrent/adjuvant and concurrent alone improved PFS, LRC, and DM too.

CONCURRENT ± ADJUVANT CHEMOTHERAPY

- Chen (Lancet Oncol 2012): 251 Stage III of IV (except T3-4N0) patients randomized to concurrent chemo-RT + adjuvant chemotherapy versus concurrent chemo-RT alone. At median follow-up of 38 months, 2-year FFS is not significantly different (86% vs. 84%). The authors do not recommend adjuvant cisplatin/5FU outside of clinical trials given no clear benefit, but this is a controversial issue.

NEOADJUVANT CHEMOTHERAPY

- Numerous older studies reported no OS advantage with neoadjuvant chemo + RT vs. RT alone including using cisplatin/5-FU (Chan IJROBP 1995), cisplatin-epirubicin-bleomycin (INCSG IJROBP 1996), cisplatin-epirubicin (Chua et al. 1998), and cisplatin-bleomycin-5-FU (Ma et al. 2001).
- Lee (Cancer 2015). 706 patients randomized into 6-arm trial: 1) induction-concurrent versus concurrent-adjuvant chemotherapy, 2) capecitabine/cisplatin (PX) in place of standard 5-FU/cisplatin (PF), and 3) accelerated versus conventional fractionation. Preliminary results at 3.3 years of follow-up suggest no significant benefit with switching from concurrent-adjuvant to induction-concurrent, more favorable toxicity with PX in place of PF, and no benefit but higher toxicities (mucositis and dehydration) with altered fractionation.
- Sun (Lancet Oncol 2016). 480 patients with Stages III–IVB (except T3-4N0) randomized to IMRT with

concurrent 100 mg/m² cisplatin every 3 weeks × 3c vs. induction TPF (docetaxel 60 mg/m², cisplatin 60 mg/m², and continuous 5FU 600 mg/m² on day 1 to day 5, every 3 weeks × 3c) followed by the same IMRT-cisplatin concurrent regimen. Induction TPF chemo improved 3-year failure-free survival (80% vs. 72%). Induction TPF increased grade 3–4 neutropenia (42% vs. 7%), leucopenia (41% vs. 17%), and stomatitis (41% vs. 35%).

EBV DNA TITERS

- Lin (NEJM 2004): 99 patients with Stages III–IV (M0) received chemotherapy followed by radiotherapy. At one week after the completion of radiotherapy, patients with persistently detectable plasma EBV DNA had worse overall survival ($p < 0.001$) and relapse-free survival ($p < 0.001$) than patients with undetectable EBV DNA.
- Leung (JCO 2008): 376 patients. On multivariate analysis, high EBV DNA (>4000 copies/mL) and low EBV DNA (≤4000 copies/mL) were predictive of OS ($p = 0.005$). EBV DNA load was better prognostic than UICC staging especially for Stage II.
- Wang (Cancer 2013): 210 NPC patients, including 99 previously reported by Lin (NEJM 2004) with Stage III–IV disease, were treated with induction chemo and RT and were followed for at least 6 years. EBV titer <1500 copies/mL had increased OS and RFS. Persistently elevated EBV titer 1 week after completion of sequential chemo-RT had worse OS, RFS.
- NRG-HN001: Patients enter either phase II or phase III study based on post-chemoradiation EBV DNA plasma titers. If EBV is undetectable, phase III randomization to cisplatin/5FU adjuvant chemotherapy versus no further treatment. If EBV is detectable, phase II randomization to cisplatin/5FU versus gemcitabine/paclitaxel adjuvant chemotherapy.

IMRT

- UCSF (Lee IJROBP 2002, 2003): 67 patients treated with IMRT to 70 Gy. Excellent 4-year OS (88%) and LRC (97%).
- Lee (JCO 2009). RTOG 0225 phase II study for Stages I–IVB using IMRT (2.12/70 Gy) and (for T2b or N+)

concurrent cisplatin → cisplatin/5-FU × 3c. Two-year locoregional control 90.5%, PFS 73%, OS 79%.

- Kam (JCO 2007): 60 patients with T1-2bN01 NPC randomized to 2D vs. IMRT. IMRT reduced 1 year observer-rated severe xerostomia (82% vs. 39%) and improved salivary flow rate. Subjective feeling of recovery not significantly different between arms.
- Pow (IJROBP 2006): 51 patients with Stage II disease randomized to IMRT vs. 2DRT. The mean parotid dose was 68 Gy for 2DRT and 42 Gy for IMRT. At 1 year, IMRT patients had improved salivary flow and surveys indicated improved physical/emotional health.

ALTERED FRACTIONATION

- Lee (Radiother Oncol 2011): 189 patients with T3-4 N0-1M0 NPC randomized to one of four treatment arms (2x2 design: radiation alone versus radiation + concurrent cisplatin and adjuvant cisplatin/5FU; conventional versus altered fractionation). Chemo-RT with altered fractionation was the winning arm with highest 5-year failure free rate of 88%.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Patient set-up supine and immobilized with head and neck thermoplastic mask or equivalent device.
- Planning CT scan obtained with IV contrast if available. A prechemo MRI is critical for definition of GTV. Use CT-MRI fusion if available.
- In every case, the entire GTV must be treated to the entire prescription dose. Except in the case of very early T1–T2 N0 tumors, it is not possible to accomplish this without exceeding normal tissue tolerances with conventional 2D planning. 3DCRT or IMRT is necessary for the final cone down.
- *IMRT volumes (Lee Radiother Oncol 2017)*:
  - *High dose clinical target volume (CTVp1)*
    - Margin from GTVp
      - GTVp + 5 mm (+/– whole NP), can reduce to minimum 1 mm (if close proximity to critical OARS)

- *High dose clinical target volume (CTVn1)*
  - Margin from GTVn
    - GTVn + 5 mm (consider 10 mm if ECE)
- *Intermediate dose clinical target volume (CTVp2)*
  - Margin from GTV
    - GTVp + 10 mm + whole NP can reduce to minimum of 2 mm (if close proximity to critical OARS)
  - Nasal cavity – posterior part
    - At least 5 mm from choana
  - Maxillary sinuses – posterior part
    - At least 5 mm from posterior wall
  - Posterior ethmoid sinus
    - Include vomer
  - Skull base
    - Cover foramen ovale, rotundum, lacerum, and petrous tip
  - Cavernous sinus
    - If T3-4 (involved side only)
  - Pterygoid fossae and parapharyngeal spaces
    - Full coverage
  - Sphenoid sinus
    - Inferior ½ if T1-2; whole if T3-4
  - Clivus
    - 1/3 if no invasion; whole if invasion
- *Intermediate dose clinical target volume (CTVn2)*
  - CTVn1 + 5 mm
  - Lymph nodes – bilateral RP, level II, III, and Va
    - Include level VIIb plus at least ipsilateral one level below the involved levels
  - Level Ib
    - Cover if involvement of submandibular gland, structures that drain to level Ib as first echelon (oral cavity, anterior half of nasal cavity), level II with ECE
- *Low dose clinical target volume (CTVn3)*
  - Levels IV and Vb down to clavicle
    - Omit if N0 or N1 based solely on RPLN involvement
- IMRT plan can be matched isocentrically to a conventional low neck field.
- *Conventional set-up* (when IMRT not available) = 3 fields (lateral opposed fields covering the primary and upper neck, with isocentric match to a low neck field). Use a

central larynx block on the low neck field and then full cord block after 42 Gy.

- *Conventional borders*: superior = generously cover sphenoid sinus and base of skull. Inferior = match at plane above true vocal cords (to block larynx in AP field). Posterior = spinous processes. Anterior = 2–3 cm anterior to GTV (and include pterygoid plates and posterior 1/3 of maxillary sinuses).
- If supraclavicular nodes involved, historically used a mediastinal 8 cm wide T field with inferior border 5 cm below the head of the clavicle.
- Use wedges and compensators as needed.

DOSE PRESCRIPTIONS

- *IMRT per RTOG 0615*: CTV70 (GTV + 5 mm) = 2.12/70 Gy, CTV56-59.4 = 1.8/56–59.4 Gy, CTV54 1.64/54 Gy in 33 fractions.
- *Conventional*: 2/42 Gy → off cord boost to 50 Gy with a posterior neck electron field → cone down to GTV + 2 cm margin to 70 Gy. For the neck, N0 = 50 Gy, nodes <3 cm = 66 Gy, and nodes ≥3 cm = 70 Gy.
- *Rotterdam NPX applicator*: optional boost after 66–70 Gy to gross disease. Use 1 week after EBRT (T1–T3 60 Gy EBRT → HDR 3 Gy × 6; T4 70 Gy EBRT → HDR 3 Gy × 4).

DOSE LIMITATIONS

- Recommend careful contouring of organs at risk. See atlas by Sun and colleagues (Radiother Oncol 2014).
- *EBRT*: partial brain 60 Gy, brainstem 54 Gy (60 Gy point dose), cord 45 Gy, optic chiasm 54 Gy, retina 45 Gy, lens 10 Gy, lacrimal gland 30 Gy, ear (sensorineuronal hearing loss) 45 Gy, parotid mean dose 26 Gy, TMJ max dose 70 Gy.
- *SRS*: brainstem 12 Gy, optic nerves or chiasm 8 Gy.

COMPLICATIONS

- Acute: mucositis, dermatitis, xerostomia.
- Late: soft tissue fibrosis, trismus, xerostomia, hearing loss, vasculopathy, osteoradionecrosis, temporal lobe necrosis, hypothyroidism, hypopituitarism (if included).

FOLLOW-UP

- H&P every 1–3 months for the first year, every 2–4 months second year, every 4–6 months years 3–5, and then every 6–12 months
- MRI at 2 and 4 months post-RT and then every 6 months or as clinically indicated
- TSH every 6–12 months
- Dental cleaning every 3 months for lifetime

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