Chapter 10
Nasopharynx

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10.1 Pearls [1, 2]

- ~86,000 annual cases worldwide. Distinct geographic distribution with high incidence in southern China and Hong Kong (25–50 cases/100,000 people), while more uncommon in the USA and Western Europe (0.2–0.5 cases/100,000 people).
- More common in men (2–3:1). Two age peaks: 15–25 years and 50–60 years.
- Strong association with EBV (70–80% of patients); other risk factors include tobacco, alcohol, and preserved or fermented food consumption.
- Higher incidence with known first-degree relative.
- Most common presenting symptoms include headache, diplopia, facial numbness (from cranial nerve involvement), and neck mass (from nodal involvement). Other symptoms can include nasal pain/obstruction, epistaxis, serous otitis media, tinnitus, hearing loss, or other cranial nerve involvement (III, IV, V, VI most common).
- Local anatomy:
  - Arises from epithelial lining of the nasopharynx.
  - Three histological subtypes: WHO I (keratinizing SCC, ~25% of US cases), WHO II (nonkeratinizing, differentiated SCC, ~12% of US

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cases), and WHO III (nonkeratinizing, undifferentiated, ~63% US of cases vs. 95% of Chinese cases). There is also a basaloid SCC, noted to be more aggressive with poor survival.
  - Anatomical borders of nasopharynx:
  - Anterior—posterior nasal septum and nasal apertures
  - Posterior—pharyngeal mucosa
  - Superior—sphenoid bone
  - Inferior—roof of the soft palate
  - The lateral wall contains pharyngeal opening of the Eustachian tubes; a protuberance (torus tubarius) is created at the posterior aspect of the orifice. Posterior to the torus tubarius is the fossa of Rosenmüller (most common primary site).
- Common pathways of local spread include along the walls of the nasopharynx, superiorly through sphenoid bone (can involve CN III, IV, V, VI), and laterally to involve parapharyngeal space (including CN IX–XII).
- High incidence of lymph node metastases at diagnosis—70–80% clinical, 90% subclinical, and up to 50% bilateral. Cervical levels II and V most commonly involved.
- Distant metastases present in 5–10%; most common sites are bone, lung, and liver.
- Medical workup:
  - H&P, focusing on assessment of cranial nerves. Physical exam requires thorough CN exam and cervical lymph node assessment
  - Fiber-optic nasopharyngolaryngoscopy
  - Basic lab work (CBC, metabolic panel, liver function tests, TSH, and EBV DNA viral load)
  - Dental and baseline speech/swallowing evaluations
- Imaging workup: Crucial to determine the extent of tumor invasion and detecting nodal metastases.
  - MRI head/neck w/wo contrast, CT neck w/ contrast, chest CT wo contrast. Additionally, strongly consider PET/CT (to assess distant metastases).
    MRI: Appear as heterogeneous enhancing mass on T1 post-contrast image; T1 pre- and T2 images reveal isointense tumor compared to muscle; also good to delineate PNI and medullary bone invasion.
    CT: Appear as soft-tissue mass; will show heterogeneous enhancement post-contrast; optimal for assessing cortical bone involvement.
    PET/CT: Both primary and nodal metastases will show FDG avidity.
- Pathology workup:
  - EBV FISH or PCR.
  - HPV and p16 can also test positive, but no prognostic/predictive value in nasopharynx cancer.
- Treatment strategies: Radiation therapy with EBRT alone for early-stage tumors (stage I). Radiation with EBRT + concurrent chemotherapy for locally advanced tumors (stage 2–4). SBRT can be used as a boost following EBRT for primary treatment, or as sole therapy in the re-irradiation setting. Surgery not typically recommended due to anatomic location.

10.2 AJCC Staging (AJCC 8th ed., 2017)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor, but EBV+ cervical node(s) involved
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* and/or adjacent soft-tissue invasion (medial, lateral pterygoid, prevertebral muscles)
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extension beyond lateral surface of lateral pterygoid muscle
*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) 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
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
0	TisN0M0
I	T1N0M0
II	T1N1M0, T2N0-1M0
III	T1-2N2M0, T3N0-2M0
IVA	T4N0-2M0, any T, N3, M0
IVB	Any T, any N, M1

10.3 Patient Selection

- Definitive setting: EBRT (5–7 weeks) followed by SBRT boost (1–6 weeks later):
  - Radiographically residual tumor.

- Re-irradiation setting:
  - Small (≤3.5 cm diameter or ≤5 cc tumor volume), single lesion preferred; node negative.
  - Biopsy or radiographic proven local persistence or recurrence.
  - Not directly encasing cavernous sinus and/or internal carotid artery or within 9 mm of optic chiasm/optic nerve (or use multiple fractions to reduce late complications).

10.4 Treatment Planning

Simulation instructions	SBRT boost • 1–6 weeks post-standard chemoradiation (EBRT) • Repeat diagnostic MRI w/wo contrast • Use adaptive planning: – Re-simulate patient—Supine, immobilized with head and neck thermoplastic mask or stereotactic frame • Planning CT performed with IV contrast, 1–3 mm slices • Fuse pretreatment MRI to adaptive CT and MRI to delineate residual tumor after initial EBRT • Post-EBRT GTV is the target (residual tumor). Re-irradiation: • Simulate supine immobilized with head and neck thermoplastic mask or stereotactic frame • Planning CT performed with IV contrast, 1–3 mm slices • Fuse updated diagnostic MRI (should be within 2 weeks of CT simulation) to planning CT to delineate recurrent tumor
Image guidance	• CyberKnife: Skull and spine tracking • Linac: CBCT
Margins	PTV = GTV + 3–5 mm
Dosimetric considerations	Dose prescribed to periphery of lesion. Goal = 95% of PTV covered by 80% IDL Depending upon technique, target shape, or proximity to critical structures, prescribing to lower IDL may be necessary. Conformity index for the PTV should be ≤2 (preferably ≤1.5).

Use T1 post-contrast MRI to aid in tumor delineation and planning. T2 sequences are helpful to distinguish between inflammation/fluid and gross tumor.

10.5 Common Dose/Fractionation Schemes

Definitive boost (EBRT + SBRT boost)

There are a range of doses used in the literature. EBRT doses typically range from 2Gy × 25 to 35 fx with SBRT boost doses ranging from 7–15 Gy × 1 fx to 12–15 Gy/3–5 fx.

Dose/Fx	Number of fx	Total dose	Notes
EBRT—2 Gy SBRT boost—11–12 Gy	EBRT—33 SBRT boost—1	EBRT—66 Gy SBRT boost—11–12 Gy	Use SBRT boost for small amount of residual tumor, away from critical OAR(s) [3]
EBRT—2 Gy SBRT boost—4–5 Gy	EBRT—33 SBRT boost—3	EBRT—66 Gy SBRT boost—12–15 Gy	For use when nearby critical OAR(s); treat boost QOD [4, 5]
EBRT—2 Gy SBRT boost—5 Gy	EBRT—25 SBRT boost—3	EBRT—50 Gy SBRT boost—15 Gy	Alternative for use when nearby critical OAR(s); treat boost QOD [4, 5]

Definitive EBRT: Hypofractionated RT-alone regimen has also been described.

Dose/Fx	Number of fx	Total dose	Notes
2.34 Gy	30	70.2 Gy	Treat QD [6]

Re-irradiation (SBRT alone)

Wide range of fractionation schedules in the literature, and depend on tumor size, dose to nearby OARs, cumulative RT already received, and time interval from previous RT.

Dose/Fx	Number of fx	Total dose	Notes
9 Gy	2	18 Gy	Treat QOD [7]
11 Gy	3	33 Gy	Treat QOD [8]
12 Gy	4	48 Gy	Treat QOD [7]
6 Gy	5	30 Gy	Treat QOD [9]
6 Gy	8	48 Gy	Treat QOD [7]
8 Gy	6	48 Gy	Treat QOD [10]

10.6 Normal Tissue Tolerances

	TG101[a] [11]	
Organ	Dmax	Volumetric
Brainstem		
• 1 fx	15 Gy	<0.5 cc
• 3 fx	23 Gy	<0.5 cc
• 5 fx	31 Gy	<0.5 cc
• DLT	Cranial neuropathy	
Optic nerves/chiasm		
• 1 fx	10 Gy	<0.2 cc

Organ	TG101[a] [11]	
	Dmax	Volumetric
• 3 fx	17 Gy	<0.2 cc
• 5 fx	25 Gy	<0.2 cc
• DLT	Neuritis	
Spinal cord		
• 1 fx	14 Gy	<0.35 cc
• 3 fx	22 Gy	<0.35 cc
• 5 fx	30 Gy	<0.35 cc
• DLT	Myelitis	
Cochlea		
• 1 fx	9 Gy	NA
• 3 fx	17 Gy	NA
• 5 fx	25 Gy	NA
• DLT	Hearing loss	

[a]At UNC we follow TG101 constraints. However, TG101 dose constraints were *not* created from nasopharynx patients who received SBRT following EBRT or SBRT alone. Thus while the constraints may not directly apply to nasopharynx patients, they are a good reference

10.7 Patient Management

1. Premedicate for SBRT with single-dose 4 mg PO dexamethasone. May consider premedicating with antiemetic (e.g., zofran 4 mg PO × 1, phenergan 12.5 mg PO × 1, 30 min before treatment) for nausea or anxiolytic (e.g., ativan 0.5-1 mg PO × 1, 30 min before treatment) for claustrophobia and/or anxiety.
2. Toxicity

   (a) Definitive (EBRT + SBRT boost)

   - Acute:
     - Skin/soft tissue (dermatitis, alopecia, xerostomia, mucositis, dysgeusia, dysphagia, odynophagia)

       Emollients (aquaphor, calendula): Remove prior to RT treatment.
       Baking soda/salt rinses up to 12x/day.
       Oral solutions (first BLM, magic mouthwash): Use prior to meals.
       Pain medication (long-acting example: fentanyl patch 25–100 mcg q72 h; short-acting example: oxycodone 5–20 mg q4-6 h).
     - Nausea/vomiting

       Zofran 4 mg q8 h: Can increase to 8 mg q8 h.
       Phenergan 12.5 mg q4–6 h: Can increase to 25 mg q4–6 h.
       Compazine 5 mg q6 h: Can increase to 10 mg q6 h.
   - Subacute/late:
     - Skin/soft tissue (ulceration, fistula, necrosis, <10%)

- Tinnitus/hearing loss (variable, worse when receiving cisplatin chemotherapy)

  Discontinue offending drug.
  Refer to neurology.

- Trismus (<10%)
- Cranial nerve neuropathy (<10%)
- Nasopharyngeal hemorrhage (<5%)
- Pharyngeal stricture/stenosis (<10%)
- Temporal lobe necrosis/ORN of skull base (<15%)
- Carotid aneurysm/blowout (~1%)

  Emergent surgery

****For above late complications, recommend referral to appropriate specialty for management (ENT, surgery, neurology, etc.).*

(b) Re-irradiation (SBRT alone)

- Acute:
  - Patients unlikely to experience symptoms during treatment.
  - In the 2–4 weeks posttreatment, patients can experience dysphagia, odynophagia, dysgeusia, fatigue, or nausea/vomiting.

Management similar to definitive treatment setting (above).

- Subacute/late:
  - Mucosal necrosis (<10%)
  - Trismus (<10%)
  - Nasopharyngeal hemorrhage (10%)
  - Pharyngeal stricture/stenosis (<15%)
  - Temporal lobe necrosis/ORN skull base (<15%)
  - Carotid aneurysm/blowout (5–10%)
  - CN neuropathies [9–12] (<15%)

****For above late complications, recommend referral to appropriate specialty for management (ENT, surgery, neurology, etc.).*

3. Recommend follow-up 1 month posttreatment to assess acute toxicity.
4. Systemic therapy:

(c) There is minimal to no data addressing the use of concurrent chemotherapy/systemic therapy with SBRT boost, in either the definitive setting or the re-irradiation setting. When used in the definitive setting, neo-adjuvant, concurrent, or adjuvant chemotherapy was frequently given with EBRT; however, its use was held during the SBRT boost. When used in the re-irradiation setting, chemotherapy is typically not given concurrently with radiation; if given at all, typically following completion of radiation.

(d) We recommend against the use of concurrent systemic therapy off-study due to the concern of increasing toxicity and lack of data on the safety of this combination.

10.8 Follow-Up

- H&P, fiber-optic nasopharyngoscopy every 2–3 months for first 2 years, q6 months years 3–5, then annually.
- PET/CT and MRI w/wo contrast at 3 months posttreatment, then q6 months for first 2 years, then as clinically indicated. Chest CT w/o contrast annually.
- If pretreatment EBV viral load is elevated, follow posttreatment EBV DNA plasma levels at 3 and 6 months, then as clinically indicated.

10.9 Relevant Literature

- There are no published guidelines as to the recommended dosing/fractionation of SBRT for both definitive boost following chemoradiation or in the re-irradiation setting; however, there are several studies demonstrating its efficacy.
- There is wide variation in these trials with regard to dose, fraction size, prescribed IDL, use of concurrent chemotherapy, and timing of when boost is delivered. Overall promising results with small, but concerning late toxicity reports.

Definitive boost setting.

Study	Patients	Treatment	Median f/u	Outcomes
Prospective studies				
Hara 2008 [3]	*n* = 82, stage IIA-IVb 85% w/ concurrent cisplatin chemotherapy during EBRT	EBRT to 66Gy + single fx SRS boost Boost 2–6 weeks post-EBRT (reimaged prior to boost) Boost: Median 11 Gy (range 7–15 Gy) × 1 fx Dose Rx to 80% IDL	40 months	98% 5-year LC 69% 5-year OS Late toxicity: Carotid aneurysm (1%), temporal lobe necrosis (12%)
Chen 2006 [4]	*n* = 64, majority stage III–IVb 60% w/ concurrent cisplatin chemotherapy during EBRT	EBRT 64–68Gy + fractionated SBRT boost Boost 1 week post-EBRT Boost: 4–5 Gy × 3 fx GTV + 2-3 mm Dose Rx to 85% IDL	31 months	93% 3-year LC 84% 3-year OS Late toxicity: No G4 toxicity; 3 pts. Died from nasal bleeding, unclear if related to SBRT

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Yamazaki 2014 [5]	*n* = 25, stage IIA–IVb Majority w/ concurrent cisplatin or 5FU chemotherapy during EBRT	EBRT to 50Gy (median) in 1.8–2Gy/fx + SBRT boost Boost: 5Gy × 3fx (median) Dose Rx to 80% IDL	28 months	71% 5-year LC 70% 5-year OS Late toxicity: G2 ulcerations, >G3, fistula (8%)
Yau 2004 [12]	*n* = 52, majority stage II–IV 23% w/ concurrent cisplatin chemotherapy during EBRT	EBRT to 66Gy + either brachytherapy or SBRT boost Boost: 7.5 Gy × 2 fx or 2.5 Gy × 8 fx Brachytherapy: ^{192}Ir HDR, median 4–10 Gy × 2–5 fx, twice weekly GTV + 3–5 mm Dose Rx to 100% IDL	36 months	**Overall**: 71% 3-year LC 82% 3-year OS **Brachytherapy**: 71% 3-year LC **SBRT**: 82% 3-year LC Late toxicity: Transient soft-tissue necrosis (3%)

Definitive EBRT

Study	Patients	Treatment	Median f/u	Outcomes
Prospective study				
Bakst 2011 [6]	*n* = 25	Dose painting EBRT w/ chemotherapy 2.34 Gy × 30 fx PTV = GTV + 1 cm	33 months	91% 3-year LC 89% 3-year OS Late toxicity: 12% temporal lobe necrosis

Re-irradiation setting

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Chua 2009 [7]	*n* = 125 Previous EBRT 66–70 Gy. ~25% concurrent chemo Tx recurrent disease w/ single vs. multiple fx SBRT Median time between recurrence 10 months	Single: 12.5 Gy median Multiple: 18 Gy/2–4 fx qod (48 Gy/4–6 fx for recurrent dx) PTV = GTV + 2-3 mm Dose Rx to 80% IDL (single fx) or 90% IDL (multiple fx) Median tumor volume 5.2 cc	40 months	**Single fraction**: 51% 3-year LC 66% 3-year OS 33% late toxicity (16% brain necrosis, 2% hemorrhage) **Multiple fraction**: 83% 3-year LC 61% 3-year OS 21% late toxicity (12% brain necrosis, 4% hemorrhage)

Study	Patients	Treatment	Median f/u	Outcomes
Seo 2009 [8]	*n* = 35 Previous EBRT + cisplatin. Median RT dose 70 Gy Median time between recurrence 26 months	Median 33 Gy/3 or 5 fx qd PTV = GTV + 2 mm Dose Rx to 80% IDL Median tumor volume 8 cc	25 months	84% 5-year LC 60% 5-year OS 5 pts. with late G4/5 toxicity (mucosal necrosis (5%) and hemorrhage (9%))
Ozyigit 2011 [9]	*n* = 51 Previous EBRT 67–70Gy + ~60% concurrent chemotherapy Tx recurrent disease w/ 3DCRT vs. SBRT Median time between recurrence 36 months	30 Gy/5 fx (SBRT) qd 60 Gy/30 fx (3D) PTV = GTV (SBRT) Dose Rx to 95–99% IDL Median tumor volume 63 cc	24 months	**SBRT**: 82% 2-year LC 64% 2-year CSS 21% late toxicity (17% carotid blowout, 12% neuropathy, 4% brain necrosis) **3D**: 80% 2-year LC 47% 2-year CSS 48% late toxicity
Wu 2007 [10]	*n* = 90 (majority had single lesion, ≤4 cm) Previous EBRT 60–74 Gy Tx w/ SBRT (7 pts. received 3D + SBRT) Median time between recurrence 23 months	Persistent dx = median 6 Gy × 3 fx qd Recurrent = median 8 Gy × 6 fx qd PTV = GTV + 2–3 mm Dose Rx to 90% IDL Tumor volume 5–6 cc	20 months	**Persistent dx**: 89% 3-year LFFS 81% 3-year DMFS 72% 3-year PFS **Recurrent dx**: 75% 3-year LFFS 67% 3-year DMFS 43% 3-year PFS Late toxicity: Mucosal necrosis (7%), G5 hemorrhage (2%), and brainstem necrosis (3%)
Pai 2002 [13]	*n* = 36 Previous EBRT 64–81Gy Tx recurrent disease w/ 3DCRT + SBRT Median time between recurrence 16 months	SBRT = median 12 Gy × 1 fx 3D = median 2 Gy × 25 fx PTV = GTV Dose Rx to 80% IDL Median tumor volume 16.8 cc	22 months	57% 3-year LC 54% 3-year OS Late toxicity: Mucosal necrosis (11%) and nasal bleeding (8%)

10.10 Summary

Again, there is wide variation in published studies with regard to dose, fraction size, prescribed IDL, use of concurrent chemotherapy, and volume irradiated. Results are promising; however, there remains a relatively high rate of grade 3/4 toxicity, including some grade 5.

10.11 UNC Experience

At our institution, we do not routinely perform SBRT boost in the definitive setting, as the LC and OS rates are similar to those of definitive EBRT alone with chemotherapy, but with a higher risk of severe late effects (carotid blowout, hemorrhage, ORN).

For patients with persistent/recurrent local disease, we re-irradiate with SBRT at 600 cGy/fx for five fractions for a total dose of 3000 cGy. Radiation is given every other day using the CyberKnife radiosurgery system. The GTV is expanded 3–5 mm to make a PTV (no CTV is created). We typically track on the skull base and prescribe to the 80% IDL.

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