Radiation for Nasopharyngeal Carcinoma

John M. Holland, MD
May 15, 2013
Nasopharyngeal Cancer
Nasopharynx Cancer “Pearls” from Hansen

- Unusual in U.S. but WHO Type III (undifferentiated) common in Southern China and Hong Kong (3rd most common tumor in Hong Kong men)
- Strongly associated with EBV (70% patients have positive titers)
- Two peak ages: 15-25 years and 50-60 years
- More common among men than women (2:1)
- Alcohol and tobacco are associate with WHO Type I (keratinizing SCC)
- 70% have clinically involved lymph nodes, 90% have subclinical nodes and 40-50% have bilateral nodes
- Other histologies include lymphoma, plasmacytomas, melanomas, rhabdomyosarcomas
## Background

<table>
<thead>
<tr>
<th>WHO type</th>
<th>Putative risk factors</th>
<th>Risk group/age affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I, keratinizing squamous cell</td>
<td>Smoking</td>
<td>Mainly affecting low-risk populations and older ages</td>
</tr>
<tr>
<td>Type II, nonkeratinizing squamous cell,</td>
<td>EBV</td>
<td>≈5% of all cases</td>
</tr>
<tr>
<td>differentiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type III, nonkeratinizing squamous cell,</td>
<td>EBV</td>
<td>Mainly affecting high-risk populations, as well as children (irrespective of level of</td>
</tr>
<tr>
<td>undifferentiated</td>
<td></td>
<td>risk in population)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Declining Incidence in Hong Kong primarily in Keratinizing Subtype felt to be related to decreased incidence of smoking
Presentation

- Most tumors will have spread to regional nodes by diagnosis

- Tumors can present with local symptoms:
  - 1) epistaxis
  - 2) nasal obstruction
  - 3) hearing loss
  - 4) serous otitis (remember to look at the nasopharynx if a patient presents with unilateral serous otitis)

- Tumors can present with regional spread:
  - 1) Nodes of Rouviere (lateral retropharynx)
  - 2) Upper Posterior neck is the “nasopharynx node”
  - 3) Upper jugular nodes
Nasopharynx Syndromes

**Jacod's**: compression of CN II-VI by extension into cavernous sinus, leading to ophthalmoplegia, blindness, and trigeminal neuralgia

**Villaret**: compression of CN IX-XII by parapharyngeal nodes, leading to difficulty swallowing (IX), altered taste (IX), unilateral Horner's (X), paralysis of sternocleidomastoid/trapezius (XI), hemiglossal paralysis (XII)

Vernet's syndrome (jugular foramen syndrome): compression of CN IX-XI by extension into jugular foramen, leading to difficulty swallowing, vocal cord paralysis, and paralysis of sternocleidomastoid/trapezius

**Trotter's triad**: unilateral hearing loss, impaired soft palate motility, and mandibular pain
Nasopharynx Cancer Workup

- Exam
  - Fiberoptic Exam: do both sides
  - Good neck exam: Pay attention to posterior neck and supraclavicular fossa

- Imaging
  - MRI is best for evaluating parapharyngeal extent
  - CT is useful if concerned about bony invasion
  - PET/CT is good for staging (distant metastatic disease in not uncommon)

- Bloodwork
  - EBV IgA/DNA titers

- Don’t forget **dental** evaluation/extractions
- **Audiology** examination since many receive cisplatin chemotherapy
Nasopharynx Anatomy
Nasopharynx Anatomy

- Borders of the Nasopharynx
  - Anterior: posterior end of nasal cavity
  - Posterior: clivus and C1-C2 vertebral bodies
  - Superior: sphenoid bone/sinus
  - Inferior: roof of soft palate

- The eustachian tube enters the lateral wall of the nasopharynx and posterior aspect of this orifice bulges creating the torus tubarius.
- The **fossa of Rosenmüller** is behind and superior to the torus tubarius and is the most common location for nasopharyngeal carcinoma.
Nasopharynx Normal Anatomy
Nasopharynx Cancer Staging AJCC 7th Edition

- **Primary**
- **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 (denotes posterolateral infiltration of tumor)
- **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, or with extension to the infratemporal fossa/masticator space
Nasopharynx Cancer Staging AJCC 7th Edition

• **Regional Spread**

• **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 (midline nodes-like medial retropharyngeal nodes-are considered ipsilateral)

• **N2**: Bilateral metastases in cervical node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa

• **N3**: Metastasis in a lymph node(s) greater than 6 cm and/or to supraclavicular fossa

• **N3a**: Greater than 6 cm in dimension

• **N3b**: Extension to the supraclavicular fossa
Nasopharynx Cancer Staging AJCC 7th Edition

- Overall Staging

- Stage I: T1N0
- Stage II: T1N1, T2N0, T2N1
- Stage III: T1N2, T2N2, T3N0, T3N1, T3N2
- Stage IVa: T4N0, T4N1, T4N2
- Stage IVb: Any TN3
- Stage IVc: Any T Any N M1
Radiation alone can be used to treat early stage tumors: T1N0, T2N0 (maybe even T1N1)

Xiao and colleagues report 5 year survival rates:
- T1N0 96.6%
- T2N0 91.3%
- T1N1 85.8%

These authors feel chemotherapy needs to be added once stage T2N1 or higher with lower overall 5 year survival (73.1%) and lower metastasis-free survival (81.2%)

IJROBP 2009; 74:1070-1076
Radiation Alone for Early Stage Nasopharynx Cancer

Overall Survival

Distant Metastasis-Free Survival

χ² = 32.28
P = 0.0000

χ² = 26.84
P = 0.0000
Radiation Alone for Early Stage Nasopharynx Cancer: IMRT alone

- Su et al report experience using IMRT alone in 198 patients with T1T2NoN1 nasopharyngeal carcinoma treated in China
- IMRT was used alone: 68 Gy delivered over 30 fractions of 2.27 cGy.
- For No patients “RT did not include the lower neck”.

- Median FUP 50.9 months
- 5 year local control 94-100%
- Overall 12 patients recurred: 4 local, 3 regional, 4 distant and 1 patient with recurrence in all 3 sites.

- There was no grade 3 or 4 xerostomia; 3% had grade 1 trismus.
- IJROBP 2012; 82: 327-333
Nasopharyngeal Cancer: Chemoradiation for Locoregionally Advanced Disease

- Intergroup Trial 0099
- Phase III Trial

- RT alone: 1.8-2 Gy fractions to 70 Gy vs.
- RT + concurrent cisplatin followed by 3 cycles cisplatin/5FU

- 193 patients eligible
- 147 evaluable: 69 RT, 78 chemoRT

- 3 year overall survival established chemoradiation as superior: 76% vs. 46%
Chemoradiation for Nasopharynx Cancer: Improved Survival over RT alone

Three year survival was 76% after chemoRT vs. 46% after RT alone (p<.001).

Al-Sarraf et al JCO 1998; 16:1310-1317
IMRT for Nasopharyngeal Cancer

- Standard Radiotherapy technique for Intergroup 0099 to treat the nasopharynx: a series of reducing (smaller) opposed lateral fields.
- Nancy Lee reported UCSF single-institution experience using Intensity-Modulated Radiotherapy (IMRT) in 2002.
- 50 received chemotherapy *ala* Intergroup 0099
- 26 received intracavitary nasopharyngeal brachytherapy boost.

- Median FUP 31 months
- 1 local failure
- 1 regional failure (Locoregional control 97%)
- 17 developed distant metastases (25%)

*IJROBP* 2002;53:12-22
UCSF IMRT Experience for Nasopharynx Cancer

Dose “painting” with IMRT
UCSF IMRT Experience for Nasopharynx Cancer

Fig. 5. Kaplan–Meier estimate of local-regional progression–free probability.

Fig. 7. Kaplan–Meier estimate of overall survival.
Nasopharynx Treatment Planning

- **Simulation**
- Make sure sites of dental extraction are healing
- Aquaplast mask for immobilization
- CT with IV contrast (if not contraindicated)
- Scan from just above the sella to the carina (start more superiorly if concern about intracranial extent of disease)

- Fuse MRI and PET to simulation CT to aid in contouring
Nasopharynx Treatment Planning

- Contouring is extensive
- Contour using Eisbruch’s guidelines
- Expansion of the GTV will often need to be trimmed to limit doses to brainstem, cord
- Do your best to keep brainstem max dose <59 Gy (QUANTEC)
- It is challenging to reach standard parotid, cochlea objectives
Nasopharynx Contouring: Eisbruch Guidelines

- “The CTV encompasses the base of skull, pterygoid plates, and superior parapharyngeal space (located lateral to the pharynx, and medial to the pterygoid muscles and the deep lobe of the parotid gland). The pterygoid muscles are encompassed in all but very early tumors. In the base of the skull, the sphenoid sinus and cavernous sinuses should be encompassed. The CTV is at least 7-8 cm wide to encompass the foramen ovale, carotid canal, and foramen spinosum that serve as potential routes for spread to the cavernous sinuses. Caudal to the primary tumor, the parapharyngeal space should be included in the CTV to approximately midtonsil level, while the retropharyngeal space is outlined as a part of the retropharyngeal lymph node CTV to the level of the hyoid bone. Posteriorly, the clivus is included, and anteriorly, the CTV includes the posterior third of the maxillary sinuses, the posterior ethmoid sinuses, and the posterior third of the nasal cavity. In cases of base of skull involvement, generous CTV margins may include the hypophysis, optic nerves, and chiasm. Limiting the dose received by these structures to 45-55 Gy (at daily fraction size <2 Gy) would be one of the objectives of planning.”

Nasopharynx Contouring: Eisbruch Guidelines

Figure 1. Delineation of the primary tumor GTV and CTV, and upper Level II CTVs, in a case of nasopharyngeal cancer, tumor stage T3. The GTV was delineated on MRI and the contours were registered with the planning CT. For treatment planning, the GTV and CTV were each expanded uniformly by 5 mm to yield the corresponding PTVs. (A) Caudal to the nasopharynx: The pharyngeal walls and parapharyngeal spaces constitute the primary tumor GTV. Level II CTVs are delineated to the base of skull bilaterally. (B-C) The clivus, foramina at the base of skull, pterygoid plates, posterior maxillary sinuses, and nasal cavity are encompassed by the CTV. (D) Cranial to the MRI-defined GTV, the sphenoid and cavernous sinuses are encompassed by the CTV.
Epstein-Barr Virus (EBV) Titers and Nasopharyngeal Carcinoma

- EBV is “present in cells from almost every primary and metastatic nasopharyngeal carcinoma, regardless of the degree of tumor differentiation or the geographic origin of the patient.”
- Lin and colleagues correlated plasma EBV load (quantitated by PCR) with risk of relapse and overall survival in 99 patients with Stage III/IV nasopharyngeal carcinoma in Taiwan.
- EBV DNA detectable in 94 of 99 (95%)
- Overall survival (P<0.001) and relapse-free survival (P=0.02) were significantly lower among patients with pretreatment plasma EBV DNA concentrations of at least 1500 copies per milliliter than among those with concentrations of less than 1500 copies per milliliter.
- Patients with persistently detectable plasma EBV DNA had significantly worse overall survival (P<0.001) and relapse-free survival (P<0.001) than patients with undetectable EBV DNA one week after the completion of radiotherapy.

Epstein-Barr Virus (EBV) Titers and Nasopharyngeal Carcinoma

Graph A: Overall Survival (\%)
- EBV DNA < 1500 copies/ml
- EBV DNA ≥ 1500 copies/ml
- P < 0.001

Graph B: Relapse-free Survival (\%)
- EBV DNA < 1500 copies/ml
- EBV DNA ≥ 1500 copies/ml
- P = 0.02
Epstein-Barr Virus (EBV) Titers and Nasopharyngeal Carcinoma
Epstein-Barr Virus (EBV) Titers and Nasopharyngeal Carcinoma
Adjuvant Chemotherapy for patients with Persistent Elevated EBV Titers after ChemoRT?

- Phase III trial from Hong Kong
- 150 patients
- Chemotherapy vs. Observation
- Adjuvant chemotherapy (gemcitabine and cisplatin)
  
  Gemcitabine 1000 mg/m² in 250 ml NS over 30 mins IV on Day 1 and 8
  Cisplatin 40 mg/m² in 1L NS over 2 h IV on Day 1 and 8
  Cycle repeated every 3 weeks for total of 6 cycles
- Estimated to accrue by July 2013
Radiation for Recurrent Nasopharynx Cancer

- Different techniques can be used to deliver radiation for locally recurrent disease
  1) Stereotactic Radiosurgery
  2) IMRT
  3) Brachytherapy

- Recurrence after definitive therapy can be late—even greater than five years after chemoRT
Radiation for Recurrent Nasopharynx Cancer

- Memorial Sloan Kettering recommends using a combination of EBRT and brachytherapy when treating locally recurrent nasopharynx cancer.
- “Nearly” all retreated with chemotherapy.
- Five-year actuarial local control, event-free survival, and overall survival rates were 52%, 44%, and 60%, respectively in this series.
- The incidence of late Grade ≥3 events in patients re-treated with EBRT alone was significantly increased compared with those receiving CMT (73% vs. 8%; p = 0.005).

IJROBP 2010; 76:130-137
Brachytherapy for Recurrent Nasopharynx Cancer

Brachytherapy performed 1-4 weeks after EBRT: 10 I-125, 2 Ir-192
“Typical” dose 20 Gy over 2 days
Stereotactic Radiotherapy for Persistent/Recurrent Nasopharynx Cancer

- Queen Mary Hospital in Hong Kong has used fractionated stereotactic radiation therapy (FSRT) to treat persistent (34) or locally recurrent (56) tumors using multiple noncoplanar arcs of 8-MV photons.
- Fractionation was 18 Gy over 3 fractions (group 1) or 48 Gy over 6 fractions (group 2).
- One-, 2-, and 3-year disease-specific survival (DSS) and progression-free survival (PFS) rates for all patients were 83%, 75%, 58%, and 73%, 60%, 55%, respectively. Three-year local failure-free survival, DSS, and PFS rates were 89%, 81%, and 72% for Group 1, and 75%, 46%, and 43% for Group 2, respectively.
- Patients with persistent disease and small tumor volumes (≤5 cc) did better than patients with recurrent disease or larger tumors.
- Seventeen patients developed late complications, including 2 with fatal hemorrhage.
- IJROBP 2007; 69:761-769
Stereotactic Radiotherapy for Persistent/Recurrent Nasopharynx Cancer: Queen Mary Hong Kong

Fig. 1. Isodose distribution using fractionated stereotactic radiation therapy (FSRT) for persistent disease at left nasopharynx occurring at 3 months after 70 Gy primary conventional radiotherapy. FSRT prescribed dose (90% isodose line) was 12 Gy in two fractions to cover the target volume. Mean dose was 3.6 Gy in two fractions to the brain stem.

Fig. 2. Isodose distribution using fractionated stereotactic radiation therapy (FSRT) for recurrent disease at right side skull base and cavernous sinus occurring in 2 years after 70 Gy primary conventional radiotherapy. FSRT prescribed dose (90% isodose line) was 48 Gy in six fractions to cover the target volume. Mean dose was 15 Gy in six fractions to the brain stem.
Nasopharynx Cancer: The Quiz!!

1. What virus is associated with nasopharynx cancer?

- A) HPV
- B) EBV
- C) HIV
- D) Kuru
Nasopharynx Cancer: The Quiz!!

1. What virus is associated with nasopharynx cancer?

Answer: EBV
Nasopharynx Cancer: The Quiz!!

2. Which subtype of Nasopharynx Cancer is most closely associated with smoking and drinking?

A) WHO Type I
B) WHO Type II
C) WHO Type III
D) WHO Live at Leeds
Nasopharynx Cancer: The Quiz!!

2. Which subtype of Nasopharynx Cancer is most closely associated with smoking and drinking?

Answer: WHO Type I: keratinizing squamous cell carcinoma
Nasopharynx Cancer: The Quiz!!

3. What percentage of NPC patients present with:

1) Clinical adenopathy
2) Subclinical adenopathy
3) Bilateral adenopathy
Nasopharynx Cancer: The Quiz!!

- What percentage of NPC patients present with:
  - 1) Clinical adenopathy (70%)
  - 2) Subclinical adenopathy (90%)
  - 3) Bilateral adenopathy (40-50%)
4. Nasopharyngeal tumors often spread to the node of Rouviere. Where is this node?

A. Medial retropharynx
B. Lateral retropharynx
C. Upper Posterior Neck
D. 82nd and Fremont
Nasopharynx Cancer: The Quiz!!

4. Nasopharyngeal tumors often spread to the node of Rouviere. Where is this node?

A. Medial retropharynx

B. Lateral retropharynx

C. Upper Posterior Neck

D. 82nd and Fremont

The “node of Rouviere” is the most superior of the lateral group of the retropharyngeal lymph nodes, and is found at the base of the skull” –Wikipedia (yeah, I’m not too proud)
Nasopharynx Cancer: The Quiz!!

5. Fill in the Blanks

- The eustachian tube enters the lateral wall of the nasopharynx and the posterior aspect of this orifice bulges creating the ________.

- The ___________ is behind and superior to the torus tubarius and is the most common location for nasopharyngeal carcinoma.
Nasopharynx Cancer: The Quiz!!

- The eustachian tube enters the lateral wall of the nasopharynx and the posterior aspect of this orifice bulges creating the torus tubarius.

- The fossa of Rosenmüller is behind and superior to the torus tubarius and is the most common location for nasopharyngeal carcinoma.
6. Name the Structures
Nasopharynx Cancer: The Quiz!!

1. Fossa of Rosenmuller  
2. Torus tubarius  
3. Eustachian tube
7. Stage this Nasopharyngeal Cancer.

- Bulky left-sided tumor extending into the left maxillary sinus and masticator space.
- Bilateral retropharyngeal adenopathy: 1.5 cm on the right; 2 cm on the left.
- 3 cm left upper posterior neck node.
Nasopharynx Cancer: The Quiz!!

Answer: T4N1 (IVa)

- **T4**: Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
- **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 (midline nodes-like medial retropharyngeal nodes-are considered ipsilateral)

Stage IVa: T4N0, T4N1, T4N2
8. Stage this Nasopharynx Cancer

- Right sided tumor erodes into the clivus and is associated with bilateral cervical adenopathy.
- Largest node on the right is 5 cm
- Largest node on the left is 4 cm
- The left node is in the supraclavicular fossa
Nasopharynx Cancer: The Quiz!!

- Answer: T₃N₃b Stage IVB

- T₃: Tumor involves bony structures of skull base and/or paranasal sinuses
- N₃b: Extension to the supraclavicular fossa
- Stage IVb: Any TN₃
Nasopharynx Cancer: The Quiz!!

9. According to Intergroup 0099, what was the three year overall survival following chemoradiation for locoregionally advanced nasopharynx cancer?

- A) 85%
- B) 75%
- C) 65%
- D) 55%
Nasopharynx Cancer: The Quiz!!

- Answer

- B. 76% (I know, that’s not 75%, but c’mon)
Nasopharynx Cancer: The Quiz!!

10. According to Eisbruch, all of the following EXCEPT one should be included in the CTV when treating nasopharynx cancer:

- A) pterygoid plates
- B) sphenoid sinus
- C) sella
- D) ipsilateral deep lobe of the parotid
Nasopharynx Cancer: The Quiz!!

- Answer: C

- The sella does not routinely need to be covered in the CTV unless there is skull base invasion
11. True or False: Pretreatment plasma EBV DNA concentrations are predictive of outcome when treating nasopharynx cancer
Nasopharynx Cancer: The Quiz!!

- Answer: True

- Overall survival ($P<0.001$) and relapse-free survival ($P=0.02$) are significantly lower among patients with pretreatment plasma EBV DNA concentrations of at least 1500 copies per milliliter than among those with concentrations of less than 1500 copies per milliliter.
Nasopharynx Cancer: The Quiz!!

12. True or False: Reirradiation for recurrent nasopharynx cancer is possible with meaningful long-term success.
Nasopharynx Cancer: The Quiz!!

• Answer: True

• Memorial Sloan Kettering reports using a combination of EBRT and brachytherapy to limit long-term complications in this population

• Five-year actuarial local control, event-free survival, and overall survival rates were 52%, 44%, and 60%, respectively in this series.
13. Which of the following is NOT seen in Trotter’s Triad?

A) Unilateral hearing loss
B) Impaired soft palate motility
C) Loss of lateral gaze
D) Mandibular pain
Nasopharynx Cancer: The Quiz!!

- Answer:
- C. Loss of lateral gaze