ARROCase
Nasopharynx Cancer

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October 20, 2016
Case: History

H&P:

• 37 yo male presents with left-sided neck mass, ear pressure, otalgia, and pain radiating down the ipsilateral neck.

• ROS:
  – + nose bleeds, numbness on the left cheek
  – - trismus, dysphagia, odynophagia, diplopia, or changes in vision

• Pertinent physical exam findings:
  – ECOG: (0) Fully active
  – HEENT: No mucosal lesions on direct/indirect examination. Poor dentition - no molars. Perforated left TM with erythematous auditory canal. Tenderness to palpation of the left post-auricular space.
  – Lymphatics: Firm, matted adenopathy of the left level II-III nodes, with palpable ipsilateral supraclavicular nodes.

• Flexible nasal laryngoscopy: ulcerated lesion of the left nasopharynx obstructing the left Eustachian tube orifice, fullness of the left fossa of rosenmuller, extending toward the soft palate and posterior pharyngeal wall with partial obstruction of the pharynx.
Common presenting signs & symptoms

- Neck mass
- Epistaxis
- Middle ear effusion/otalgia/decreased hearing
- Headache/pain
- Nasal congestion and drainage
- Trismus
- Cranial nerve deficits
  - Petro-sphenoidal syndrome (CN III-IV, VI): Oculomotor signs/symptoms
  - Retro-parotidian syndrome (CN IV-XII): Enophthalmos, ptosis, miosis
Case: Imaging

CT Neck

MRI Orbit, Face, & Neck

- Nasopharyngeal mass
- Enlarged retro-pharyngeal lymph node
- Enlarged contralateral retro-pharyngeal lymph node

Multiple enlarged bilateral cervical lymph nodes (levels II – V), including supraclavicular node (level IV)
Work-Up & Evaluation

- H&P including complete head & neck physical exam
  - Tobacco history
- Flexible nasopharyngeal fiber-optic laryngoscopy
- Labs
  - EBV titers
- Biopsy of the primary site or FNA of neck
- MRI w/ contrast – include skull base, nasopharynx, and neck to clavicles
- CT Neck & Chest, as clinically indicated
- PET-CT (especially for non-keratinizing histology, endemic phenotype, N2 or N3, and stage III – IV)
- Medical oncology consultation
- Dental evaluation
- Nutrition/GI evaluation
- Speech and swallow evaluation
- Audiology evaluation
Differential Diagnosis of malignancy for nasopharyngeal mass

If small nasopharyngeal mass and confined to the mucosa:
- Prominent, but normal adenoidal tissue
- Nasopharyngeal lymphoma
- Early primary nasopharyngeal malignancy

If larger nasopharyngeal mass +/- involvement of the skull base:
- Primary nasopharyngeal malignancy
- Adenoid cystic carcinoma
- Papillary adenocarcinoma
- Melanoma
- Plasmacytoma
- Lymphoma
- Chordoma/Chondrosarcoma
- Meningioma
- Rhabdomyosarcoma/other sarcoma
- Metastases
Case: Pathology

• He underwent US-guided FNA of the left cervical neck mass
• Pathology: poorly differentiated carcinoma
  – Pleomorphic epithelioid cells in a background of lymphocytes
  – + cytokeratin
  – p16 negative
  – EBV in-situ hybridization negative
  – Neuron specific enolase negative
Nasopharynx Cancer

Incidence:
• 5 per 1 million in the USA
• 100 – 400 per 1 million in Asia/Africa

Risk Factors:
• Salted or pickled foods
• Metal dust
• Epstein-Barr virus (EBV)
• Smoking
• HLA/Genetic

Presenting signs/symptoms:
• Palpable cervical adenopathy
  – 70% cN+
  – 90% pN+ (50% bilateral)
• Nasal discharge
• Hearing loss
• Trismus
• Cranial neuropathy (CN II – XII)
Anatomy: Skull Base & Nasopharynx

- Pterygopalatine Fossa (PPF)
- Sphenoid Sinus
- Clivus*
- Soft Palate*
- Choanae*
- C1 – C2*

* anatomic boundaries of the NPx
Anatomy: Skull Base & Nasopharynx

Parapharyngeal space

Cavernous sinus

Foramen rotundum
WHO Grading System
Nasopharyngeal Carcinoma

• **WHO I: keratinizing squamous cell carcinoma**
  – 20% prevalence
  – Associated with smoking, HPV
  – Poor LC
  – Lower risk of DM

• **WHO II: non-keratinizing, squamous cell carcinoma**
  – (A) Differentiated type
  – (B) Undifferentiated type
  – 30 – 40% prevalence

• **WHO III: undifferentiated, lympho-epithelial, or basaloid squamous cell carcinoma**
  – 40 – 50% prevalence
  – Most strongly associated with EBV
  – Better LC
  – Higher risk of DM
AJCC Staging System

Nasopharyngeal Carcinoma

**Tumor**

**T1:** confined to NPx, OPx, and/or nasal cavity without parapharyngeal extension  
**T2:** parapharyngeal extension  
**T3:** bony structures of skull case of paranasal sinuses  
**T4:** intra-cranial extension, cranial nerves, HPx, orbit, or with extension to infra-temporal fossa/masticator space

**Nodes**

**N1:** unilateral, ≤ 6 cm, above SCLV fossa; or uni/bilateral RP nodes, ≤ 6 cm  
**N2:** bilateral, ≤ 6 cm, above SCLV fossa  
**N3a:** > 6 cm  
**N3b:** SCLV fossa*

**Metastases**

**M1:** any distant metastasis

*SCLV fossa is the triangular region defined by the 3 points:  
(1) Superior margin of the sternal end of clavicle  
(2) Superior margin of lateral end of clavicle  
(3) Point where neck meets shoulder

**Abbreviations:**  
NPx: nasopharynx, OPx: oropharynx, HPx: hypopharynx, SCLV: supraclavicular
**AJCC Staging System²**

**Nasopharyngeal Carcinoma**

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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</thead>
<tbody>
<tr>
<td><strong>N0</strong></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IVA</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>II</td>
<td>II</td>
<td>III</td>
<td>IVA</td>
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<tr>
<td><strong>N2</strong></td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IVA</td>
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<tr>
<td><strong>N3</strong></td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
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<tr>
<td><strong>M1</strong></td>
<td>IVC</td>
<td>IVC</td>
<td>IVC</td>
<td>IVC</td>
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</tbody>
</table>
Case: Management

• cT1 cN3b cM0, stage IVB, p16- EBV- poorly differentiated nasopharyngeal carcinoma

• Consultation with Otolaryngology, Medical Oncology, Radiation Oncology

• Treatment options for T2-4 or N+ include:
  – Concurrent chemoradiation → +/- adjuvant chemo
  – Induction chemo → concurrent chemoradiation
Case: Management

• This patient received:
  – Concurrent CRT to 70 Gy in 33 fractions with weekly cisplatin 40 mg/m$^2$
  – Adjuvant/consolidation cisplatin/5-FU
Radiation Planning

• Simulation:
  – Supine, long mask, IV contrast:
  – Co-register with MRI +/- PET-CT

• Radiation Dose/Fractionation:
  – PTV1: 69.96 Gy in 33 fractions (2.12 Gy/Fx)
  – PTV2: 59.4 Gy in 33 fractions (1.8 Gy/Fx)
  – PTV3: 54 Gy in 33 fractions (1.63 Gy/Fx)
  – Consider hyper-fractionation if dose to optic structures/brainstem would be otherwise unacceptable
Radiation Technique

- IMRT
- Proton beam radiotherapy
- Brachytherapy
  - Intracavitary boost
  - Consider for recurrent disease
  - Possible dose escalation of early/advanced primary tumors
Radiation Contouring

- PTV1 (69.96 Gy)
  - Gross disease

- PTV2 (59.4 Gy)
  - High risk subclinical disease:
    - Sphenoid sinus
    - Cavernous sinus
    - Skull base
    - Clivus
    - Posterior 1/3 of maxillary sinus
    - Posterior 1/3 of nasal cavity
    - Pterygopalatine fossae
    - Parapharyngeal space
    - Retropharyngeal space
    - Soft palate

- PTV3 (54 Gy):
  - Elective nodal coverage:
    - Retrostyloid space
    - Bilateral IB – V (can omit IB, if N0)

Contouring references:
- e-contour http://econtour.org/cases/2
Dose Constraints

Critical normal structures (higher priority):
- Brainstem, optic nerves, chiasm: Max < 54 Gy
- Spinal cord: Max < 45 Gy
- Mandible/TMJ: Max < 70 Gy
- Temporal lobes: Max < 60 Gy

Other normal structures (lower priority):
- Parotid glands: Mean ≤ 26 Gy in at least one gland,
  or at least 20 cc of the combined volume of both parotid glands to receive < 20 Gy,
  or at least 50% of one gland to receive < 30 Gy
- Tongue: Max < 55 Gy
- Inner/middle ears (especially with concurrent Cisplatin): Mean < 50 Gy
- Eyes: Mean < 35 Gy
- Glottic larynx: Mean < 45 Gy
- Lens: ALARA
Case: Target Volumes

PTV70

PTV59.4

GTVp

PTV54

GTVn
Case: Isodose Distribution
Case: Isodose Distribution
Case: Isodose Distribution
Case: Dose Volume Histogram
# Treatment Algorithm

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment options</th>
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<tbody>
<tr>
<td>T1 N0</td>
<td>• Definitive RT</td>
</tr>
<tr>
<td>T1 N+</td>
<td>• Concurrent CRT → +/- adjuvant chemo</td>
</tr>
<tr>
<td>T2-4 N0</td>
<td>• Induction chemo → concurrent CRT</td>
</tr>
<tr>
<td>T2-4 N+</td>
<td></td>
</tr>
<tr>
<td>Tx Nx M1</td>
<td>• Chemotherapy (platinum-based)</td>
</tr>
<tr>
<td></td>
<td>• Concurrent CRT</td>
</tr>
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</table>
Chemotherapy

Evidence for Concurrent + Adjuvant ⁴⁻⁶

<table>
<thead>
<tr>
<th></th>
<th>Intergroup 0099</th>
<th>Al Sarraf et al., JCO 1998</th>
<th>RTOG 0225</th>
<th>Lee et al., JCO 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, phase III</td>
<td></td>
<td>Phase II</td>
<td></td>
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<tr>
<td><strong># Patients</strong></td>
<td>147</td>
<td></td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>RT alone vs. CRT</td>
<td></td>
<td>RT +/- Chemo (for ≥T2 and/or N+)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>Primary tumor: 70 Gy</td>
<td>Lymph nodes:</td>
<td>Primary Tumor: 70 Gy at 2.12 Gy/Fx</td>
<td>Intermediate risk: 59.4 Gy at 1.8 Gy/Fx</td>
</tr>
<tr>
<td></td>
<td>N0: 50 Gy</td>
<td>N+ ≤2cm: 66 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N+ &gt;2cm: 70 Gy</td>
<td></td>
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<tr>
<td><strong>Chemotherapy</strong></td>
<td>Concurrent: cisplatin 100 mg/m² q3weeks</td>
<td>Adjuvant: cisplatin 80 mg/m² + 5-FU 100 mg/m²/day q4weeks x 4</td>
<td>Concurrent: cisplatin 100 mg/m² q3weeks</td>
<td>Adjuvant: cisplatin 80 mg/m² + 5-FU 100 mg/m²/day q4weeks x 4</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>3-year PFS: 24 → 69% (p &lt; .001)</td>
<td>3-year OS: 46 → 76% (p &lt; .001)</td>
<td>2-year PFS: 72.7%</td>
<td>2-year OS: 80.2%</td>
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<tr>
<td><strong>Comments</strong></td>
<td>Large # of WHO type I</td>
<td>RT alone arm performed poorly</td>
<td>94% WHO types II – III</td>
<td>IMRT is feasible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Closed early due to SS improved survival with chemo</td>
<td>No excessive toxicity</td>
<td></td>
</tr>
</tbody>
</table>

- Results of Intergroup 0099 study confirmed by Chan *et al.*. CRT with weekly cisplatin vs. RT alone led to 5-year OS improvement 59 → 70%
Chemotherapy

Evidence for Induction:

• No demonstrated benefit of induction chemo
• NCCN Guidelines category 3 recommendation

Evidence for Adjuvant⁷:

• No demonstrated benefit for adjuvant chemo following definitive RT or CRT, although long term data not yet available
• NCCN Guidelines category 2B recommendation
Follow Up for Nasopharyngeal Cancer

- H&P + complete H&N physical exam +/- mirror/fiberoptic exam
  - q1-3 months for year 1
  - q2-6 months for year 2
  - q4-8 months for years 3 – 5
  - Yearly for years > 5

- Imaging for signs/symptoms
- TSH yearly (if irradiated)
- Speech/swallowing/dental/hearing evaluations
- Consider EBV-DNA monitoring
Nasopharynx Clinical Pearls

- Uncommon in the United States
- High likelihood of distant metastases
- Rarely, parotid nodal relapses can occur
- Due to the anatomic location, RT traditionally used over surgery
- Local control with RT alone of early (T1 – T2) tumors 80 – 90%
- Local control with RT alone of T3 – T4 tumors 30 – 65%
- Concurrent cisplatin-based chemo + RT has been shown to improve OS
- No evidence to support induction chemotherapy
- Little evidence to support adjuvant chemotherapy, although awaiting further results of Chen et al. phase 3 randomized trial
- RT technique is IMRT with simultaneous integrated boosts to 70 Gy, 59.4 Gy, and 54 Gy


