ARROCase: Occult Primary of the Head and Neck

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Case: History

- 62yo male with slow growing, painless left neck mass for 7 months
- ROS negative except for decreased appetite and minimal weight loss
Case: History

• PMH: left knee arthroscopic surgery, tubulovillous adenoma on c-scope
• PSH: left knee arthroscopy 1981
• FH: colon cancer - cousin
• SH: 40PY smoking history, quit 3 years ago; 6-12 beers/day; h/o cocaine use; no IVDA; works as a mover
• NKDA
• No prior chemo or radiation therapy
Case: Imaging

Enlarged jugulodigastric lymph node, 3.9cm x 2.5, max SUV 15.9
Workup & Evaluation

- H&P including complete head and neck exam, skin exam and fiberoptic exam
- Radiographic Studies
  - Chest imaging
  - CT of the head and neck
    - If equivocal, MRI
  - FDG PET-CT
- Laboratory Studies
  - CBC, CMP, TSH
- Dental, nutrition, speech and swallow evaluations
Workup & Evaluation

• Direct Endoscopy and Directed Biopsies
  – EUA, pan-endoscopy and directed biopsies of OPX and any sites with clinical suspicion
  – FNA preferred over core needle biopsy of the cervical node
    • Lower likelihood of seeding
  – HPV, EBV testing suggested for squamous cell carcinoma or undifferentiated histology
    • EBV testing, if positive, would suggest closer evaluation of nasopharynx
  – Tonsillectomy +/- lingual tonsillectomy
  – Consider thyroglobulin, calcitonin, PAX8, TTF1 staining for adenocarcinoma or undifferentiated tumors
Case: Pathology

- Direct laryngoscopy and nasal endoscopy, left palatine and lingual tonsillectomy, BOT biopsies, left neck node dissection of levels II-IV (1/37+)

- Pathology for positive level IIA node:
  - Squamous cell carcinoma, poorly differentiated
  - no ECE
  - p16 positive
  - EBV negative

- Primary areas of clinical concern all negative
Occult Primary of the H&N

- ~3-5% of all H&N cancers are of an unknown primary
- OPX is the presumed site of origin
  - Tonsils and base of tongue (80%)
- ~10% of pts present with bilateral neck disease
- T0 (not Tx) is the assigned T stage if no primary is found
## AJCC Staging System: Occult Primary

### Table 1

**American Joint Committee on Cancer (AJCC)**  
**TNM Staging Classification for the Lip and Oral Cavity**  
(7th ed., 2010)  
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease* (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (oral cavity) Tumor invades adjacent structures (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery</td>
</tr>
</tbody>
</table>

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

### Regional Lymph Nodes (N)

| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension |
| N2 | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N2a | Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N3 | Metastasis in a lymph node more than 6 cm in greatest dimension |

### Distant Metastasis (M)

| M0 | No distant metastasis |
| M1 | Distant metastasis |

### Histologic Grade (G)

| GX | Grade cannot be assessed |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Undifferentiated |

*Continued...*

**Overall Stage IVA (pT0pN2aM0)**
Case: Management

• This patient received:
  – RT only with IMRT to 60Gy in 30 fractions to the left neck
  – 54Gy in 2Gy x 27 fractions to the right neck and 1.8Gy x 30 fractions to the OPX
  – NPX was not included as pathology was EBV negative
Radiation Planning

• Simulation:
  – Supine with neck extended, immobilize with thermoplastic mask
  – Consider mouthpiece, wire scars, consider bolus near skin
  – IV contrast if no contraindications
  – Fuse diagnostic imaging

• Radiation Dose/Fractionation:
  – High risk areas: 66Gy in 30fx or 70Gy in 35fx
  – Intermediate risk areas: 60Gy in 30fx or 63Gy in 35fx
  – Low risk areas: 54Gy in 30fx or 56Gy in 35fx
Radiation Technique

• IMRT preferred, with image guidance if available
Radiation Contouring

- GTV = gross disease based on exam and imaging
- CTV high risk = GTV + margin for subclinical disease (5-10mm)
- CTV intermediate risk:
  - Central: CTV for central structures, nodal stations and HPV/EBV. Historically included entire pharynx and larynx
  - Neck: Bilateral IB-V and RP if bilateral neck involvement. Ipsilateral IB-V and RP if only ipsilateral neck involvement
- CTV low risk = uninvolved contralateral II to IV nodes (cannot omit)
- PTV = CTV + 3-5mm margin, depending on image guidance
# Treatment Algorithm

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0, cN1</td>
<td>• Neck dissection (preferred)</td>
</tr>
<tr>
<td></td>
<td>• Definitive RT</td>
</tr>
<tr>
<td></td>
<td>• Definitive chemoradiation</td>
</tr>
<tr>
<td>T0, cN2-3</td>
<td>• Neck dissection</td>
</tr>
<tr>
<td></td>
<td>• Definitive chemoradiation</td>
</tr>
<tr>
<td>Postop T0, pN1, no ECE</td>
<td>• Adjuvant RT</td>
</tr>
<tr>
<td></td>
<td>• Observation</td>
</tr>
<tr>
<td>Postop T0, pN2-3, no ECE</td>
<td>• Adjuvant RT (preferred)</td>
</tr>
<tr>
<td></td>
<td>• Adjuvant chemoradiation</td>
</tr>
<tr>
<td>Postop with ECE</td>
<td>• Adjuvant chemoradiation (preferred)</td>
</tr>
<tr>
<td></td>
<td>• Adjuvant RT</td>
</tr>
<tr>
<td>M1</td>
<td>• Platinum-based combination chemo (preferred)</td>
</tr>
<tr>
<td></td>
<td>• Clinical trial</td>
</tr>
<tr>
<td></td>
<td>• Palliation with RT or surgery</td>
</tr>
<tr>
<td></td>
<td>• Supportive care</td>
</tr>
</tbody>
</table>
# Dose Constraints

<table>
<thead>
<tr>
<th>Structure</th>
<th>Type</th>
<th>Volume/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>Tolerance dose</td>
<td>Entire brainstem $&lt;54$Gy</td>
</tr>
<tr>
<td>Chiasm</td>
<td>Max dose</td>
<td>$&lt;60$Gy</td>
</tr>
<tr>
<td>Ears: Cochlea</td>
<td>Mean dose</td>
<td>$&lt;45$Gy ($&lt;35$Gy if pt treated with cisplatinum)</td>
</tr>
<tr>
<td>Eyes: Lens</td>
<td>Max dose</td>
<td>$&lt;7$Gy</td>
</tr>
<tr>
<td>Eyes: Optic nerve</td>
<td>Max dose</td>
<td>$&lt;55$Gy</td>
</tr>
<tr>
<td>Larynx</td>
<td>Max dose</td>
<td>$&lt;66$Gy</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Mean dose</td>
<td>$&lt;30$Gy</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>Mean dose</td>
<td>$\leq 26$Gy in at least one gland, or at least 50% of one gland to receive $&lt;30$Gy</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>Mean dose</td>
<td>$&lt;39$Gy</td>
</tr>
<tr>
<td>Mandible</td>
<td>Max dose</td>
<td>$&lt;70$Gy</td>
</tr>
</tbody>
</table>
Case: Isodose Distribution
Case: Dose Volume Histogram
Follow Up for Occult Primary H&N

- PET-CT every 3 months after definitive RT/CRT
- If suspicion for residual neck disease, consider neck dissection
- After adjuvant RT, posttx baseline imaging of head and neck within 6 months
- If asymptomatic, H&P and NPL
  - every 1-3 mo for yr 1
  - every 2-6 mo for yr 2
  - every 4-8 mo for yr 3-5, then annually
- TSH every 6-12 mo
- Low threshold for biopsy if suspect emergence of primary
- Nutrition, dental, speech, swallow, hearing and smoking cessation
Selected Studies

• Indications for withholding RT (Coster, Red J 1992)
  – 24 patients with occult primary, unilateral neck disease underwent curative resection
  – 25% had recurrence in dissected neck; 5/6 of recurrences were in those with ECE+
  – For pN1 and no ECE, surgery alone is sufficient; if pN2+ or ECE, consider adjuvant RT
Selected Studies

• Occult Primary Site Detection (Cianchetti, Laryngoscope 2009)
  – 236 patients with occult primary underwent CT, MRI, panendoscopy with directed biopsies, PET, and/or tonsillectomies
  – Occult primary was detected in 53% with majority of these found in the tonsil (45%) and BOT (44%)

• Bilateral Tonsillectomy (Koch, Otolaryngol Head Neck Surg 2001)
  – Oncologic rationale for bilateral tonsillectomy in head and neck SCC of unknown primary
  – Rate of contralateral tonsil primary approaches 10%
Selected Studies

• EORTC 22931 and RTOG 9501 (Bernier, Head Neck 2005)
  – CRT improved DFS and LRC in patients with ECE or positive margins, but provided only trend for improvements in stage III-IV, PNI, LVSI, and/or enlarged level IV to V nodes
  – Patients with ≥2 involved nodes without ECE as their only risk factor did not benefit from chemo

• Cancer of Unknown Primary Treated with IMRT (Shoushtari, Red J 2001)
  – Definitive IMRT and neck dissection results in excellent nodal control and OS, DFS with acceptable toxicity for patients with T0N1 or T0N2a disease without ECE
References


