Case Presentation – Unknown Primary Squamous Cell Carcinoma of Head and Neck

The Greater Baltimore Medical Center
Metastatic Cancer to the Neck From Unknown 1º Site

- WHO definition: histologic diagnosis of metastases without diagnosis of 1º tumor
- 2-9% of all head and neck cancers
- Estimates suggest 50% of metastatic cancer to the neck from an unknown primary site to be SCC

June 4, 2012
Background

- Workup should clearly involve a search for the primary site
- $1^\circ$ tumor is prognostic indicator
Background

• Consider the possibility:
  – Neck mass is “primary” site of cancer
  – Spontaneous regression of true primary w/ residual metastases
  – Primary tumor is present, but quiescent
Background

- Importance of PE performed by Head and Neck Surgeon
- FNA of neck mass
- PET-CT (in patients w/ negative CT and endoscopic findings, PET Revealed primary in 29-39%\textsuperscript{7,8}

June 4, 2012
Treatment Options:

- Depends on whether source is found during workup:
  1) If primary site identified, then treatment is directed at primary tumor origin
  2) Alternatively, true unknown primary: comprehensive ND, post-op radiation to involved neck and possible mucosal sites
Case Presentation #1: DP

- 42 yo male
- Hx right neck mass reportedly since 12/11
- PMH: HTN, peptic ulcer dz
- PSH: none
- FH: noncontributory
- SH: tobacco use since age 15, with 12 pack years. Drinks socially
- Meds/Allergies: None
Case Presentation #1: DP

- PE: Normal oral cavity and oropharynx with soft base of tongue
- FNA of neck mass showed SCC
- Prior to scan, patient was unknown primary SCC of head and neck
PET-CT: DP

- 2.9 cm right level II LNw/ intense uptake and SUV max of 12.9
- Second 8mm node asjacent
- Subtle asymmetric uptake in R posterior BOT (normal variation)
- No mass on CT/enhanced CT
• OHNS read of PET-CT was potential uptake in right tonsil

• Staging:
  - 1° Tumor: T1 2 cm or less
  - LN: N2b multiple ipsilateral LN, none more than 6 cm
  - Metastases: M0 none
Surgical Treatment: DP

• DL w/ bx, PEG, Extraction of 4 wisdom teeth, TORS radical tonsillectomy, R SND 1-4, L SND 1, L SMGT

• Path: Histologically labeled moderately differentiated invasive squamous cell carcinoma
Future Treatment: DP

• Awaiting radiation therapy (5 weeks after surgery)
Case Presentation #2: JL

- 54 yo female
- L neck mass during TMJ eval 3/2012
- PMH: Graves dz, migraines, TMJ, GERD
- FH: a fib, stroke, emphysema, bipolar, DM, skin cancer
- SH: 4 yr use of 1 ppd 30 yrs prior
- Meds/Allergies: nexium, pain med, synthroid
Case Presentation #2: JL

- PE: Normal oral cavity and oropharynx with soft base of tongue
- L Neck Level II nodes deep to SCM
- CT showed left sided lymphadenopathy, no other possible sites of 1°
• Level II LN enlargement
• Mildly asymmetric left BOT with increased uptake of FDG
• Potential source for SCC – L BOT
• Patient currently a TxN2bMx
Surgical Treatment: JL

• **If 1º Source Unknown**: Bilateral tonsillectomy, possible lingual tonsillectomy, SND, PEG, Gland transfer

• **If 1º Source Known**: 1º chemoradiation
References


Radiation Oncology issues in Patients with Metastatic Cervical Carcinoma of Unknown Primary (MCCUP)
NCCN Guidelines™ Version 2.2011
Occult Primary

**PATHOLOGIC FINDINGS**

**WORKUP**

**DEFINITIVE TREATMENT**

Primary found

- Treat as appropriate (See Guidelines Index)

Node level I, II, III, upper V

- Examination under anesthesia (EUA)
- Palpation and inspection
- Biopsy of areas of clinical concern and tonsillectomy
- Direct laryngoscopy and nasopharynx survey

Node level IV, lower V

- EUA including direct laryngoscopy, esophagoscopy
- Chest/abdominal/pelvic CT (or PET-CT if not previously performed)

Adenocarcinoma of neck node, thyroglobulin negative, calcitonin negative

- Levels I-III
  - Neck dissection + parotidectomy, if indicated
  - RT f to neck ± parotid bed

- Levels IV, V
  - Evaluate for infraclavicular primary
  - Neck dissection, if indicated

Poorly differentiated or nonkeratinizing squamous cell or NOS or anaplastic (not thyroid) of neck node or Squamous cell carcinoma of neck node

See Definitive Treatment (OCC-3)
What are the Advantages to Surgery?

• Accurate Staging (up 34-57% of patients are upstaged)
• Decision for post-treatment therapy is based on actual, rather than presumed, pathologic findings
• N1 patients with good pathologic features may be observed....
What are the Advantages to Primary XRT or CRT

- No surgery
- Possibility for only one definitive therapy to be administered with hopefully less side effects
How Does Treatment Modality Affect Outcome??

- Meta-analysis
- Only studies with 5-yr survival outcomes included
- 18 studies with 1,726 patients
- 6 studies reported Extracapsular Extension

Balaker AE et al., Laryngoscope. 2012, April 26
How Does Treatment Modality Affect Outcome??

• Five Year Survivals:
  – N1: 61%
  – N2a: 63%
  – N2b: 43%
  – N2c: 38%
  – N3: 26%

• Outcomes based on EC:
  – 57% (with) versus 82% (without), p = 0.01 (Only 6/18 studies)

• Outcomes based on Treatment:
  – Surgery followed by XRT or CRT 52% vs Definitive CRT 47% (p = NS)
Surgery for N1 Disease

- 117 Patients at Mayo Clinic with CUP between 1965 and 1987
- Of these, 24 patients underwent curative resection of all gross disease with no adjuvant therapy
  - 14 were N1
  - 6 were N2a
  - 3 were N2b
  - 1 was N3
- 8 patients had ECE
- 6/24 patients (25%) developed a recurrence
  - 5/6 had ECE
  - 4/6 had N2a disease or higher
  - Both of the patients that were N1 and recurred had ECE
- Conclusion
  - Patients who are N1 that have no ECE may undergo dissection alone without adjuvant radiation
  - All other groups should receive adjuvant radiation due to high risk of local recurrence

# Surgery for N1 Disease

**Table 2.** Recurrence pattern and salvage based on initial therapy for N1–N2a patients.

<table>
<thead>
<tr>
<th>Recurrence site</th>
<th>EXC ($n = 11^*$)</th>
<th>RND ($n = 13^*$)</th>
<th>XRT ($n = 10^*$)</th>
<th>EXC+XRT ($n = 10^*$)</th>
<th>RND+XRT ($n = 4^*$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Primary</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neck and primary</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Salvaged</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The number in patients represents the total number of patients by treatment category with N1–N2a disease.

Abbreviations: EXC, excisional biopsy; RND, Radical neck dissection; XRT, radiotherapy.

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Iganej et al., Head and Neck: March 2002
Radiotherapy for N1 Disease

• Mendenhall compared 11 N1 patients who underwent node dissection and adjuvant radiation to 64 N1 patients undergoing irradiation alone
  – Irradiation + radiotherapy showed initial control in 10/11 patients (91%)
  – Irradiation alone showed initial control in 59/64 patients (92%)
• If a patient is unable to undergo surgery, radiation alone for N1 disease shows similar control rates to surgery with radiation

Erkal et al., IJROBP: 50(1); 2001
Do We Need to Address the Mucosal Sites/Contralateral Neck?
Unilateral vs Bilateral Irradiation

- 352 patients with CUP
- 277 were managed with bilateral neck irradiation and elective irradiation of sites in the nasopharynx, hypopharynx and larynx
- 26 received ipsilateral nodal irradiation only
- Patients treated with ipsilateral neck radiation compared to those receiving bilateral neck radiation had a 1.9-fold higher risk of recurrence in the head or neck (51 versus 27 percent, p = 0.05)
- Ipsilateral nodal irradiation also had a trend toward lower five year disease-specific survival (28 versus 45 percent).

Grau et al., Radiotherapy and Oncology: 2000 (55)
Table 2  Treatment outcomes following various therapeutic approaches (reference numbers are given in superscript)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Surgery alone (mainly neck dissection) (%)</th>
<th>Surgery and ipsilateral neck irradiation (%)</th>
<th>Surgery and bilateral neck/mucosal irradiation (%)</th>
<th>Radiotherapy alone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary emergence rate</td>
<td>32&lt;sup&gt;23&lt;/sup&gt;</td>
<td>7&lt;sup&gt;79&lt;/sup&gt;</td>
<td>2&lt;sup&gt;79&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>44&lt;sup&gt;76&lt;/sup&gt;</td>
<td>12&lt;sup&gt;27&lt;/sup&gt;</td>
<td>3&lt;sup&gt;23&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>54&lt;sup&gt;26&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44&lt;sup&gt;76&lt;/sup&gt;</td>
<td>4&lt;sup&gt;73&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>66&lt;sup&gt;62&lt;/sup&gt;</td>
<td></td>
<td>8&lt;sup&gt;76&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Nodal relapse</td>
<td>24&lt;sup&gt;77&lt;/sup&gt;</td>
<td>20&lt;sup&gt;76&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0&lt;sup&gt;76&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21&lt;sup&gt;77&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>50&lt;sup&gt;69&lt;/sup&gt;</td>
<td></td>
<td>9&lt;sup&gt;25&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Distant metastases</td>
<td></td>
<td></td>
<td>14&lt;sup&gt;77&lt;/sup&gt;</td>
<td>43&lt;sup&gt;73&lt;/sup&gt;</td>
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<td>17&lt;sup&gt;73&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>18&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td>Five-year disease free survival</td>
<td></td>
<td></td>
<td>54&lt;sup&gt;72&lt;/sup&gt;</td>
<td>28—45&lt;sup&gt;26&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>66&lt;sup&gt;6&lt;/sup&gt;</td>
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<td></td>
<td>74&lt;sup&gt;25&lt;/sup&gt;</td>
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<tr>
<td>Five-year overall survival</td>
<td>47&lt;sup&gt;76&lt;/sup&gt;</td>
<td>41&lt;sup&gt;27&lt;/sup&gt;</td>
<td>22&lt;sup&gt;78&lt;/sup&gt;</td>
<td>0&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>37&lt;sup&gt;99&lt;/sup&gt;</td>
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<td>48&lt;sup&gt;79&lt;/sup&gt;</td>
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<td>60&lt;sup&gt;25&lt;/sup&gt;</td>
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<td>52&lt;sup&gt;31&lt;/sup&gt;</td>
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<td>53&lt;sup&gt;76&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>67&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Squamous cell and undifferentiated carcinoma included; surgery: excisional biopsy in the majority of cases.
<sup>b</sup> 28% for ipsilateral neck irradiation, 45% for irradiation of bilateral neck and mucosa.
<sup>c</sup> Only N1 cases included.
Table 2. Reported results of comprehensive and limited radiotherapy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Unilateral radiotherapy (2, 3, 5, 8, 42, 43)</th>
<th>Comprehensive radiotherapy (3, 5, 7, 34-41, 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median mucosal primary emergence rate (range)</td>
<td>8% (5–44)</td>
<td>9.5% (2–13)</td>
</tr>
<tr>
<td>Median neck relapse rate (range)</td>
<td>51.5% (31–63)</td>
<td>19% (8–49)</td>
</tr>
<tr>
<td>Median distant metastases rate (range)</td>
<td>38% (only given in Ref. 8)</td>
<td>19% (11–23)</td>
</tr>
<tr>
<td>Median 5-year overall survival rate (range)</td>
<td>36.5% (22–41)</td>
<td>50% (34–63)</td>
</tr>
</tbody>
</table>

EORTC trial examining this issue closed in 2004 w/o outcomes

Incidence of Mucosal Recurrence

- Erkal et al. reporting on 126 patients treated for an unknown primary at the University of Florida
- Similar 5 year rate of mucosal recurrence for known and unknown primaries
- Suggests that mucosal irradiation significantly reduced risk of primary site failure in patients with unknown primaries
- Or patients with unknown primaries have a much lower risk of secondary head and neck cancer developing subsequently
How do we get away from the toxicities of this???
We do this.....
Eliminate Prophylactic Larynx and Hypopharynx Treatment

- 17 patients with CUP were treated with larynx sparing radiotherapy previously described from 1997-2002.
- 16/17 patients had follow-up for at least 2 years.
- No patients developed SCC in a head and neck site.
- 1/17 patients developed persistent nodal disease (6%).
- 1/17 patients had recurrent nodal disease 1 year after completing RT (6%).
- 5 year cause specific and overall survival rates were 88% and 82% respectively.

Barker et al., Am J of Clin Onc: 28(5); 2005.
<table>
<thead>
<tr>
<th>Primary Site</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsillar fossa</td>
<td>25 (43)</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>23 (39)</td>
</tr>
<tr>
<td>Pyriform sinus</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Posterior pharyngeal wall</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Lateral pharyngeal wall</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vallecula</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Suprahyoid epiglottis</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Other Diagnostic Considerations

- **EBV**
  - In-situ hybridization for EBV-1 RNA or PCR of genomic EBV DNA may be considered on nodal FNA tissue to aid in differentiation of nasopharyngeal carcinoma
  - This workup would be more helpful in young patients with poorly differentiated SCC found in a cervical node

- **HPV ISH or p16 staining**
  - Detection may be useful in determining if the primary has origin in the oropharynx
Why Tailor Mucosal Radiation

- No survival benefit
- Some studies show equivalent primary emergence with just neck irradiation
We know XRT-induced dysphagia increases with increasing dose to pharyngeal constrictors with a probable threshold dose of 45 Gy.
PRINCIPLES OF RADIATION THERAPY

Definitive RT:
- Conventional fractionation:
  - Gross Adenopathy: 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 weeks
  - Mucosal dosing: 50-66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size and use of chemotherapy. Consider higher dose to 60-66 Gy to particularly suspicious areas
  - Neck: Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

Concurrent chemoradiation:
- Conventional fractionation:
  - Gross adenopathy: ≥ 70 Gy (2.0 Gy/fraction)
  - Mucosal dosing: 50-60 Gy (2.0 Gy/fraction) to putative mucosal primary sites. Consider higher dose to 60-66 Gy to particularly suspicious areas
  - Neck: Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

IMRT is a preferred technique when targeting the oropharynx to minimize the dose to critical structures, especially the parotid glands.
We Use IMRT to Reduce Toxicity

### Table 5. Incidence of acute toxicity by grade in patients receiving intensity-modulated radiotherapy (IMRT) and in historical control patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dysphagia</th>
<th>Mucositis†</th>
<th>Radiation dermatitis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G≤2</td>
<td>G3</td>
<td>G≤2</td>
</tr>
<tr>
<td>IMRT patients (n = 22)</td>
<td>21 (95.5%)</td>
<td>1 (4.5%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Historical controls (n = 18)</td>
<td>9 (50%)</td>
<td>9 (50%)*</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.003</td>
<td>0.82</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### Table 6. Late toxicity by grade scored after at least 6 months of follow-up

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dysphagia</th>
<th>Xerostomia*</th>
<th>Taste alteration</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G0</td>
<td>G1–2</td>
<td>G3</td>
<td>G1–2</td>
</tr>
<tr>
<td>IMRT patient (n = 18)</td>
<td>5 (27.8%)</td>
<td>13 (72.2%)</td>
<td>0</td>
<td>15 (88.2%)</td>
</tr>
<tr>
<td>Historical control (n = 15)</td>
<td>7 (46.6%)</td>
<td>4 (26.7%)</td>
<td>4 (26.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Xerostomia and taste alteration were assessed in 17 patients.
† One patient with xerostomia Grade 0 was included.

What about Chemotherapy?

Unknown primary not included in post-op trials; we extrapolate
Review of utility of chemotherapy in MCCUP is limited to small retrospective reviews, but little benefit has been discerned and larger studies are needed.

Late Grade 3+ Dysphagia: 41% vs 11%
6 mo PEG dependence: 28% vs 4%
Conclusions

• Although there are distinct advantages to surgery, XRT or CRT are viable treatment options for patients with MCCUP.

• Mucosal irradiation may decrease primary emergence, but at a cost.

• Tailoring of therapy based on HPV, EBV, node level, clinical history, and judicious use of chemotherapy are all ways to mitigate unwarranted toxicity in these patients.