Squamous Cell Carcinoma of the Neck with Unknown Primary

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Disclosure

Nothing to disclose

Objectives

• Definition
• Presentation
• Evaluation
• Management options
• Treatment outcomes
• Prognostic factors
**Unknown Primary - Definition**

Malignant neoplasm metastatic to cervical lymph nodes without an identifiable primary tumor following a comprehensive evaluation

Focus - Squamous cell carcinoma

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**Unknown Primary**

- Can be confusing to patients and family
- Take time to explain evaluation algorithm and treatment options
- Don’t overwhelm
- Try to guide patient in selection of best option for him or her
Unknown Primary

- Incidence difficult to glean due to variability in definition and diagnostic algorithms
  - 1.5% Rodel et al; Ann ORL, 2009
  - 2.4% Haas et al; Eur Arch ORL, 2002
  - 1.7% Grau et al; Radiother Oncol, 2000
- Decreasing due to more diagnostic rigor
- Failure to identify primary:
  - small size
  - cryptic location
  - tumor regression

Presentation

Issing et al; Eur Arch ORL, 2003
Grau et al; Radiother Oncol, 2000

- Neck mass 94-100%
- Pain 9%
- Weight loss 7%
- Dysphagia 4%
- M : F = 75% : 25%
- Mean age 55
Dictum: Neck Mass In Adult Is Cancer Until Proven Otherwise

Lymph Node Involvement
Grau et al; Radiother Oncol, 2000
The Surgically Violated Neck

Evaluation

• Progressive, can be time-consuming
• Detection of primary related to thoroughness of search
Physical Examination

• Complete head and neck examination
• Fiberoptic nasopharyngoscopy
• Narrow band imaging
  optical color-separation filter is used to narrow the bandwidth of spectral transmittance; lesions with well-developed microvasculature are well visualized

Hayashi et al; Jpn J Clin Oncol, 2010
Shinozaki et al; Head Neck, 2012
Ryu et al; Head Neck, 2013

Narrow Band Imaging

Hayashi et al; Jpn J Clin Oncol, 2010
Physical Examination

• Tongue protrusion
• Look for mucosal lesions, asymmetry
• Palpate oropharynx for masses, induration
Lymph Node Level

- Location of neck node(s) may provide information regarding location of primary

In general:
- Level I - not OP
- Levels II, III - suggest OP primary
- Level IV - thyroid, infraclavicular primary
- Level V - NP

Fine Needle Aspiration Biopsy

- Accurate for diagnosis
- If cystic, send fluid for cell block
- U/S guidance may help to target solid component
- Immunohistochemical stains
  - Accurate for excluding lymphoma
    Onofre et al; Diagn Cytopathol, 2008
- EBV detection – nasopharyngeal primary
  Lee et al; Head Neck, 2000
- HPV detection – oropharyngeal primary
  Vent et al; Head Neck, 2013
  Weiss et al; Head Neck, 2011
  Begum et al; Clin Cancer Res, 2007
CT Scan / MRI

- May help to identify primary tumor
  - defined lesion; asymmetry

- Useful for node assessment
  - location: level(s), contralateral, retropharyngeal
  - characteristics: size, necrosis, cystic, ECS

- Cystic node - branchial cleft cyst confusion most related to tonsil primary (64%)
  Thompson and Heffner; Cancer, 1998

CT Scan - Cystic Right Neck Node
Cystic Node
Goldenberg et al; Head Neck, 2008

- 100 neck dissections
- 20 cystic nodes
- Primary site:
  - 10 base of tongue
  - 7 tonsil
  - 3 unknown primary
- 87% HPV-16 positive by in situ hybridization
PET/CT Scan - Benefits

- Primary detection rates 25-35%
  Miller et al; Arch OHNS, 2005
  Silva et al; J Laryngol Otol, 2007
  Johansen et al; Head Neck, 2008
- May direct more attention to a specific area
- May provide more accurate staging:
  extent of regional disease
  detection of distant metastases
- May identify second primary tumor
**PET/CT Scan - Limitations**

- In general, unlikely to reveal primary not found with imaging studies, endoscopy, biopsies, tonsillectomy (1/47=2.1%) Cianchetti et al; Laryngoscope 2009
- Tumor volume threshold (5mm) necessary for detection
- False positives:
  - Physiological uptake lymphoid tissue, salivary glands
    - 12%  Fogarty et al; Head Neck, 2003
    - 13%  Johansen et al; Head Neck, 2008
  - Prior biopsy may cause uptake
    - 50%  Johansen et al; Head Neck, 2008
Examination Under Anesthesia and Direct Laryngoscopy

- Palpate for mass, induration
- Visual inspection for lesions: bleeding, friable, ulcerated, erythematous
- Magnification, videoendoscopy helpful
- Transoral laser microsurgery increases yield
  Karni et al; Laryngoscope, 2011
- TORS Abuzeid et al; Head Neck, 2011
- Directed biopsies NP and hypopharynx - low yield if no visible lesion
Transoral Laser Microsurgery

Karni et al; Laryngoscope, 2011

• N = 30 with unknown primary
• Microscope detection of abnormal appearing tissue; laser cuts made
• TLM in 18
  94% detected
• Traditional EUA in 12 (p<.001)
  25% detected
**Tonsillectomy**

- Extensive epithelial surface with crypts
- Thin section histopathology
- Occult primary detection:
  - 26% Lapeyre et al; IJROBP, 1997
  - 39% McQuone et al; Laryngoscope, 1998
  - 35% Mendenhall et al; Head Neck, 1998
- Contralateral tonsil:
  - 10% Koch et al, OHNS, 2001
  - 23% Kothari et al, Br J OMFS, 2007

**Bilateral Tonsillectomy**
Robotic Base of Tongue Resection
TORS Lingual Tonsillectomy

Mehta et al; Laryngoscope, 2013

• Lingual tonsils removed with tongue musculature as depth limit
• Effective for detecting primary
• Mean diameter = 0.9 cm
• 8/9 were p16 positive

Hopkins unpublished data 66% yield

Fluorescence Image-guided Surgery

• Indocyanine green (ICG)
• Excitation of fluorescence generated by a near infrared light source
• Good detection rate and sensitivity for breast cancer, malignant melanoma, and gastrointestinal tumors
Open Neck Biopsy

- Endoscopic evaluation for primary first
- Primary site identification may obviate need for open neck biopsy
- Frozen section analysis
- Plan for selective or modified radical neck dissection if frozen section is positive for metastatic SCCa

Lymph Node Histopathology

- Histopathologic features may provide information to indicate primary
- Lymphoepithelial - nasopharynx
- HPV-16 in situ hybridization and P16 immunohistochemistry - reliably establish oropharyngeal origin

Begum et al; Clin Cancer Res, 2003
Primary Identification

- Greater than 80% identified with systematic evaluation
- Most common sites:
  - Tonsil
  - Base of tongue
  - Pyriform sinus

Guntinas-Lichius; Acta Otolaryngol, 2006
Issing et al; Eur Arch Otorhinolaryngol, 2003

Primary Identified

- Management as appropriate for site and extent of disease
- Allows option of surgical resection
  - eg. TLM or TORS
- Better definition of primary tumor target volume
- Reduced radiation field
  - eg. reduced dose to larynx
- Assists post-treatment surveillance
Management Principles

• Neck node excisional biopsy is not sufficient treatment
• Timely treatment is important
  - particularly if neck surgically violated

Management

• Therapy options  **NCCN Guidelines**
  - type of treatment
    ND, XRT, Chemo/XRT
  - extent of treatment
    ND type, potential primary sites, ipsilateral vs. bilateral neck XRT
• Individualize
• Weigh treatment side effects against benefits
Neck Dissection - Type

- Modified radical recommended by most
- Role of selective neck dissection unclear
  24% SND Patel et al, Arch OHNS, 2007
Treatment Outcomes - Issues

- Lack of prospective, randomized trials
- Retrospective studies
- Small patient numbers
- Different patient populations
- Different inclusion criteria
- Patient selection factors

Treatment Outcomes - Endpoints

- Primary emergence rate
- Regional control
- Survival
Primary Site Emergence

- Primary site emergence 5 to 10%
- Similar rate for second primary UADT cancers
  Aslani et al; Head Neck, 2007
- Increased with surgery alone:
  Iganej et al, Head Neck, 2002
  32% vs. 9%
  Grau et al; Radiother Oncol, 2000
  54% vs. 15%

Regional Control – Single vs. Combined Therapy
Iganej et al; Head Neck, 2002
Neck Excisional Biopsy

• Excellent regional control:
  - if no residual disease
  - timely post-op XRT

• Regional control rates:
  100% Colletier et al; Head Neck, 1998
  95% Mack et al; IJROBP, 1993

Survival - Neck Dissection vs. Node Biopsy
Aslani et al; Head Neck, 2007

\[ p = .64 \]
Survival - Single Modality Therapy vs. Combination Therapy

- Conclusions difficult due to selection bias
- Surgery or XRT alone may have been given for more favorable nodal stage
- Multiple studies show survival benefit with combination therapy for advanced disease:
  - Iganej et al; Head Neck, 2002
  - Guntinas-Lichius et al; Acta Oto-L, 2006

Radiation Therapy Strategies

- Unilateral radiation therapy
  - ipsilateral neck
- Comprehensive radiation therapy
  - bilateral necks and pharyngeal axis
**Limited XRT vs. Comprehensive XRT**  
*Nieder et al, IJROBP, 2001*

<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>
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<tbody>
<tr>
<td>Median mucosal primary emergence rate (range)</td>
<td>8% (5–44)</td>
<td>9.5% (2–13)</td>
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<tr>
<td>Median neck relapse rate (range)</td>
<td>51.5% (31–83)</td>
<td>19% (8–49)</td>
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<tr>
<td>Median distant metastases rate (range)</td>
<td>38% (only given in Ref. 8)</td>
<td>19% (11–23)</td>
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<tr>
<td>Median 5-year overall survival rate (range)</td>
<td>36.5% (22–41)</td>
<td>50% (34–63)</td>
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**Conclusions:**

- No difference in primary emergence rates
- Regional control and survival appear better with comprehensive XRT than with ND with post-op XRT, or XRT alone

**Survival – Extent of XRT**  
*Beldi et al; IJROBP, 2007*
Survival

• Survival generally favorable despite advanced Stage III and IV disease
• 65 to 75% 5-year survival
  Colletier et al; Head Neck, 1998
  Erkal et al; Radiother Oncol, 2001
  Johansen et al; Head Neck, 2008
• Favorable survival despite advanced stage - HPV-related

UCSF - Surgery/XRT vs. XRT/Chemo

74% p16 positive
Prognostic Factors

- Nodal stage
- Extracapsular Spread
- Nodal level

Erkal et al; IJROBP, 2001
Beldi et al; IJROBP, 2007
Patel et al; Arch OHNS, 2007

UCSF – Survival by Nodal Stage

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<tr>
<th>Nodal Stage</th>
<th>Fraction Surviving</th>
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<tbody>
<tr>
<td>N1</td>
<td>1</td>
</tr>
<tr>
<td>N2a</td>
<td>1</td>
</tr>
<tr>
<td>N2b</td>
<td>0</td>
</tr>
<tr>
<td>N3</td>
<td>0</td>
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Total Survival (months)
Outcomes

• Surgery alone – higher primary emergence
• Combination therapy provides improved regional control and survival than surgery or XRT alone for advanced disease
• Comprehensive XRT may provide survival benefit over limited-field XRT
• More morbidity with comprehensive XRT however

Summary

• SCC of unknown primary - uncommon malignancy
• Thorough evaluation beneficial to identify primary tumor
• HPV association demonstrated
• Combination therapy appears better than single modality treatment for advanced disease
• Survival generally favorable
• Nodal stage, level, and ECS prognostic factors