Management of H&N Unknown PRIMARY Cancer:
Robotics to Personalized Medicine

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Disclosure

- Proctor for Intuitive Surgical
Cancer of unknown primary

- By definition presents with metastatic disease
- In the H&N: cervical adenopathy
- Classically older patient
Presentation / Diagnosis

• Most common complaint
  – Painless neck mass (often cystic)
  – Adult neck masses are cancer till proven otherwise

• Sore throat
• Dysphagia
• Dysarthria
Diagnosis

• Guided by the index of suspicion
• Physical exam including palpation of the oropharyngeal structures
• Look for the “bloody glove” sign
• Mirror exam and/or flexible laryngoscopy
• FNA biopsy of neck nodes can be very helpful
Occult primary tumors

• Definition
  – Requires a thorough H&N examination,
    • Negative imaging studies
    • Negative exam under anesthesia with targeted biopsies
  – “Rare” disease: thought to represent 2-4% of SCCHN
Is this problem more frequent now?

- Rising trend in HPV + disease
- Patients have smaller primary tumors and larger nodal disease
- This diagnosis seems to be more common now
- Data from UPMC & FCCC-ASTRO/AHNS abstract

![Graph showing incidence of UP SCCHN/yr from 1990's to 2010's](image-url)
Where’s the primary?

- Index of suspicion for anatomy that harbors the occult primary

- Think about
  - Waldeyer’s Ring
  - Hypopharynx
  - Infraclavicular sources
    - Lung
    - Esophagus
Anatomy of the oropharynx

Anterior inferior limit
circumvallate papillae
Anterior superior limit
junction of hard and soft palate

Lateral limit
lateral pharyngeal walls

Posterior limit
posterior pharyngeal wall

Inferior limit
vallecula and inferior base of tongue
Lymphatic drainage of the oropharynx

- Primary echelon
  - Internal jugular
  - Retropharyngeal
- Level V spread is rare
- Base of tongue & lateral walls
  - Level 2-3
- Posterior pharynx
  - Rouviere’s node

Figure 76-7 Location of medial and lateral retropharyngeal nodes. (From Field CR: The head and neck. In Haagensen CD and others, editors: The lymphatics in cancer. Philadelphia, 1972, WB Saunders, p 56. By permission of the publisher.)
Staging

• Imaging is a valuable adjunct to the physical exam
  – CT with contrast
  – PET/CT to evaluate for metastases
  – MRI with contrast for (pre-)vertebral invasion
• Operative laryngoscopy allows definitive staging and sometimes treatment planning.
• Tissue diagnosis is essential, larger biopsies allow for molecular testing
Imaging

- Cross-sectional imaging
  - CT
  - MRI
  - PET/CT
- PET/CT has ~37.5% success rate
  - Sensitivity & specificity of 84.5%
“Novel” Imaging

Fakhry et al Oral Oncology, 50(7): 640 – 645, 2014
Management

• Need to identify the primary site
  – Facilitates staging
  – Potentially improves enrollment in clinical trials

• Allows us to plan for definitive therapy

• Almost all HPV + tumors originate in the oropharynx
HPV and carcinogenesis

• HPV is a known contributor to cervical dysplasia and carcinoma
• Dr. No-Hee Park: identified similarity between cervical/vaginal mucosa and OP mucosa
• Dr. Maura Gillison: described the association between HPV (types 16/18) and OP SCCa
• Most common histology is basaloid squamous carcinoma
  – In the context of HPV prone anatomic regions
Human Papillomavirus

- DNA virus
- 100 distinct sub-types
- Cutaneous & mucosal
- High-risk
  - Cervical cancer, OPC
  - Subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58
- Low-risk
  - Anogenital warts, laryngeal papillomatosis
  - Subtypes 6, 11
HPV-16 Genome

• Early region
  – E6: inactivates p53
  – E7: inactivates pRb
    • pRb inactivation induces over-expression of p16

• Late region
  – L1, L2: capsid proteins necessary for viral persistence

• Regulatory region
  – Replication/gene expression
Surgical approaches HPV +

- Identification of the primary requires a panendoscopy
- Imaging can guide where to take the biopsies
- Palatine tonsillectomy is recommended
Palatine Tonsillectomy

• Bilateral tonsillar malignancies have been reported (10%)

• Post-treatment follow up may be easier with bilateral tonsillectomy

• Tonsillectomy allows the pathologist to submit the entire specimen
  – Need to communicate with your pathologist!
Success with endoscopy

• Several studies have shown that the success rate of panendoscopy and tonsillectomy +/- imaging is 17-40%

• Why is it important?

• Where do we miss the primary?
Survival for UPCa HN

- Dependent on N-stage
- N1: 69% at 5 years
- N2: 58%
- N3: 30%
Importance of finding the primary

• In the absence of identification
  – XRT or chemoXRT to the entire Waldeyer’s Ring
  – Potentially larynx also

• Toxicity
  – Dysphagia
  – Odynophagia
  – Xerostomia
WHERE ARE WE MISSING THE PRIMARY?
Lingual tonsils

- Part of Waldeyers Ring
- Lymphoid tissue
- Not encapsulated
  - Unlike the palatine tonsils
- Can we submit the entire lingual tonsil?
Robotic base of tongue surgery
Robotic Lingual Tonsillectomy

Resection specimen

Post-operative image, 6 months
Pittsburgh Experience

- TORS for unknown primary
- Twenty-two evaluable cases
- Average LOS: 1.2 days
- No need for feeding tubes or tracheotomies
- All tolerating some P.O. on POD 1
- 1/23 (9%) bleeding POD 7-10
- All had lingual tonsillectomy
- 6 had concurrent tonsillectomy
- 19/22 (86%) success rate
- HPV +: 100%
- 9/22 (41%) complete resection
- Mean size: 1.03 cm

Mehta et al Laryngoscope Jan 2012
TORS PEARLS AND PITFALLS

• TORS is an excellent option for many patients
• Functional outcomes are acceptable
• HOWEVER, there are pitfalls
BLEEDING

• Most feared complication
  – Intraoperative
  – Post-operative

• Avoidance is the preferred method

• Related to surgeon experience
Bleeding after TOS

• Pollei et al JAMA Oto 2013
• Retrospective review
• 906 cases treated with transoral surgery
• Post-operative hemorrhage evaluated as
  – Minor
  – Major
  – Severe
Bleeding after TOS

- Post-operative bleeding occurred in 5.4% of cases
- 67% of these cases required operative intervention
- **Severe bleeding rate: 1.1%**
- Transcervical external carotid system ligation was performed in 15% of patients
- There was no impact on bleeding rate or severity
- No difference between Robotic or Laser surgery
Center based Experience

• Surgeon experience/volume is important

• Bleeding rate seems to trend down with experience

Figure 3. Postoperative transoral robotic surgery–related complications.
• 11/147 (7.5%) patients experienced post-operative bleeding
• 9/147 (6%) required re-operation
• Average time to bleed was 8 days
• Anti-thrombotic treatment - significant
Anatomy is the basic science of surgery

-Anonymous
Anatomic complexity
Styloglossus muscle

- Styloglossus muscle (SGM) and stylopharyngeus muscle are key landmarks that delineate the vascular anatomy
- Form the ‘styloid diaphragm’
- Vascular structures are encountered lateral to the plane of the styloid diaphragm.
SGM & vascular- External view

Medial / intraoral
Intraoral view
Intraoral view
Variants of the external carotid

Dehiscence through the SGM and SPM
Dangerous Variant of ECA
Pittsburgh Experience

- 224 cases of TORS for benign and malignant disease

- Bleeding classified as minor/intermediate/major/severe

<table>
<thead>
<tr>
<th>Hemorrhage Severity (Grade)</th>
<th>Percentage of Total Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>1.79</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.34</td>
</tr>
<tr>
<td>Major</td>
<td>4.46</td>
</tr>
<tr>
<td>Severe</td>
<td>2.23</td>
</tr>
<tr>
<td>All Grades</td>
<td>9.82</td>
</tr>
</tbody>
</table>

Dr. Raj Mandal, U. Duvvuri et al – unpublished data
Single surgeon experience

• Learning curve appears to be about 50 cases
• Data may be biased as larger tumors are tackled
End vessel ligation may help
Airway Protection

Inability to Protect Airway
Secondary to Altered Mental Status,
Severe Dysphagia/Odynophagia,
Any Other Cause

Yes
- Major 0%
- Intermediate 0%
- Minor 0%
- Severe 75%

No
- Major 100%
- Intermediate 100%
- Minor 100%
- Severe 25%

Dr. Raj Mandal et al – unpublished data
Impact of finding the primary

- Retrospective review
- University of Pittsburgh 1980-2012
- Found (67) vs not found (69)
- Significant improvement in survival
- Independent of N stage
- HPV not accounted for
- Similar data reported by Haas et al
Lingual Tonsillectomy

• Can be performed with Transoral Laser Microsurgery (TLM)
  – Karni et al Laryngoscope 2012
  – Hinni et al Head Neck 2013
• Resection of the lingual tonsil allows for complete pathologic evaluation
• Identification of the primary may improve oncologic outcomes
  – Should lead to better targeting of adjuvant therapy
Management of the neck

• Nodal dissection is useful to reduce tumor burden
• Selective neck dissection is usually sufficient
• Dictated by the ultimate treatment paradigm
  – Can we de-escalate therapy?
  – Can we eradicate all disease?
Nodal Dissection & ECS

• Does nodal dissection eliminate or reduce adjuvant treatment?
  – Eliminate chemotherapy
  – De-escalate radiation dose

• ECS is still an indication for adjuvant CRT
  – Recent data suggest that ECS may not be as important in HPV + disease
Wash U Data

• 153 pts with HPV + disease
• Treated surgically
• Postoperatively some had CRT others had XRT
• ECS was not associated with worse outcomes
• However, ECS needs to be clarified
  – Microscopic
  – Minimal ECS
  – Gross extranodal extension
Towards personalized medicine

WHAT’S NEXT?
Just When You Thought You Knew Everything!

- No comprehensive mutational study reported to date in HNSCC
- 93 paired HNSCC tumor/blood DNA from independent individuals were submitted to the Broad Institute for whole exome sequence analysis
- 1 tumor failed DNA sequencing
- 18 tumors were excluded from analysis due to having less than 10 mutations identified (presumed to have substantial normal tissue contamination)
- 74 tumors with whole exome sequence data for analysis
- Now extended to the TCGA analysis with ~400 tumors
Lower Mutation Rates in HPV Positive Tumors

<table>
<thead>
<tr>
<th></th>
<th>HPV Negative</th>
<th>HPV Positive</th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
<td>4.54</td>
<td>2.38</td>
</tr>
<tr>
<td>Median</td>
<td>2.98</td>
<td>1.50</td>
</tr>
</tbody>
</table>
Genes that regulate squamous differentiation are commonly mutated.
Correlation of *PIK3CA* mutation or amplification with increased expression of p110 alpha (p=0.0027), pAKT(T308) (p=0.0360), and pAKT(S473) (p=0.0104) in 165 HNSCC tumors. Expression of total and phosphorylated proteins was assessed by reverse phase protein array (RPPA), amplification was determined by SNP array and mutation evaluated by whole exome sequencing (WES).
Table 1: Percent *PIK3CA*-mutated HNSCC tumors in multiple cohorts.

<table>
<thead>
<tr>
<th>HNSCC Cohorts</th>
<th>% <em>PIK3CA</em> mutated tumors</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>HPV-Positive</td>
<td>HPV-Negative</td>
</tr>
<tr>
<td><em>Stransky et al.</em></td>
<td></td>
<td>27.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3/11 cases)</td>
<td>(3/63 cases)</td>
</tr>
<tr>
<td><em>Agrawal et al.</em></td>
<td></td>
<td>25.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1/4 cases)</td>
<td>(2/28 cases)</td>
</tr>
<tr>
<td><em>TCGA</em></td>
<td></td>
<td>30.0%</td>
<td>18.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9/30 cases)</td>
<td>(39/210 cases)</td>
</tr>
<tr>
<td><em>Chicago</em></td>
<td></td>
<td>20.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11/55 cases)</td>
<td>(1/65 cases)</td>
</tr>
<tr>
<td><em>Pittsburgh-HPV Cohort</em></td>
<td></td>
<td>25.0%</td>
<td><em>Not applicable</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(18/72 cases)</td>
<td></td>
</tr>
</tbody>
</table>

**Av. % Tumors with *PIK3CA* mutation**

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<thead>
<tr>
<th></th>
<th>24.4%</th>
<th>12.3%</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(42/172 cases)</td>
<td>(45/366 cases)</td>
</tr>
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</table>
PIK3CA Mutation Enhances Sensitivity to PI3K Pathway Inhibition
Table 3: PI3K pathway inhibitors and their respective targets.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target(s)</th>
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<tbody>
<tr>
<td>BYL-719</td>
<td>p110α</td>
</tr>
<tr>
<td>BKM-120</td>
<td>p110α/β</td>
</tr>
<tr>
<td>PX-866</td>
<td>p110α/β</td>
</tr>
<tr>
<td>BEZ-235</td>
<td>mTOR, p110α/β</td>
</tr>
<tr>
<td>GSK-690693</td>
<td>AKT Kinase</td>
</tr>
<tr>
<td>MK-2206</td>
<td>AKT Translocation</td>
</tr>
<tr>
<td>OSI-127</td>
<td>TORC1/2</td>
</tr>
<tr>
<td>RAD001</td>
<td>mTOR</td>
</tr>
</tbody>
</table>
**PIK3CA** Mutation or High p-AKT Sensitizes HNSCC Patient Tumourgrafts to Treatment with a PI3K/mTOR Inhibitor

**A**
HPV-Positive Patient Tumourgraft with **PIK3CA** mutation

**B**
Patient Tumourgrafts

- **#1**
- **#2**

**p-AKT** (T308)

**AKT**

**Tubulin**

**C**
Patient Tumourgraft **#1** (high p-AKT)

**D**
Patient Tumourgraft **#2** (low p-AKT)

![Graphs showing tumor growth and protein expression](image-url)

- **P=0.002**
- **P=0.020**
- **P=0.300**
T0-4a, N1-3
HPV+ OPSCC
Amenable to TORS

n = 46-54

Induction Chemotherapy
3 cycles

- Cisplatin 75 mg/m²/q3week
- Paclitaxel 90 mg/m²/week
- BYL719 daily

9 weeks

TORS

Risk-Stratified IMRT

- pCR or pT1-2N0-1 (-) margin, no ECE
- Observe

- Close margin, 2-4 LN, or PNI/LVI
  - 60 Gy IMRT

- (+) margin, ECE, or ≥ 5 LN
  - 66 Gy IMRT + CDDP

*FDG/PET-CT scan
Future directions

• The management of unknown primary cancer is evolving
• Identification of the primary tumor site is important
• The initial results with robotic surgery unknown primary carcinoma is encouraging
• Prospective trials will be useful in defining the role of TORS