Salivary Gland Malignancies

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Disclosures

- Advisory board:
  - Bayer Oncology

- Educational funding:
  - Stryker
  - Medtronic
  - Ethicon
Outline

- Overview and molecular findings in salivary gland cancers
- Surgical management
- Radiation therapy

Salivary Gland Cancers

- Mucoepidermoid
- Adenoid cystic
- Adenocarcinoma
- Acinic cell
- Polymorphous adenocarcinoma
- Epithelial-myop epithelial
- Clear cell
- Basal cell adenocarcinoma
- Sebaceous adenocarcinoma
- Lymphoepithelial
- Secretory
- Intraductal
- Oncocytic
- Salivary duct
- Myoepithelial
- Carcinoma ex
- Poorly differentiated
- Carcinosarcoma
- Squamous cell
- Sialoblastoma

World Health Organization, 2017
### Fusions define salivary cancer

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Translocation</th>
<th>Gene</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid</td>
<td>t(11;19)</td>
<td>CRTC1-MAML2</td>
<td>Mostly low-intermediate grade</td>
</tr>
<tr>
<td></td>
<td>t(11;15)</td>
<td>CRTC3-MAML2</td>
<td></td>
</tr>
<tr>
<td>Adenoid Cystic</td>
<td>t(6;9)</td>
<td>MYB-NFIB</td>
<td>MYB also upregulated without translocation</td>
</tr>
<tr>
<td></td>
<td>t(8;9)</td>
<td>MYBL1-NFIB</td>
<td></td>
</tr>
<tr>
<td>Clear Cell Carcinoma</td>
<td>t(12;22)</td>
<td>EWSR1-ATF1</td>
<td></td>
</tr>
<tr>
<td>Secretory Carcinoma</td>
<td>t(12;15)</td>
<td>ETV6-NTRK3</td>
<td>Druggable</td>
</tr>
<tr>
<td>Carcinoma-ex</td>
<td>t(8q12)</td>
<td>PLAG1</td>
<td>Similar to pleomorphic adenoma</td>
</tr>
<tr>
<td>pleomorphic</td>
<td>t(12q14-15)</td>
<td>HMGA2</td>
<td></td>
</tr>
</tbody>
</table>

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**Survival Probability (%)**

- **MEC**
- **Adenocarcinoma**
- **ACC**
- **Other rare carcinomas**

Baddour HM et al, JAMA OHNS 2016
Treatment

- SURGERY
  - Facial nerve
  - Neck management
- Adjuvant therapy
  - Radiation
  - Radiation + chemotherapy

Surgical approach

- Wide local excision
  - Clear margins – site dependent
- Neck dissection
  - Elective versus therapeutic
- Balance with functional outcome
  - Nerve preservation when possible
Operative Discussion:
Facial Nerve Monitoring

- Eisele et al (2010):
  - Identification of facial nerve: reoperation, radiation, extensive malignancy, retrograde approach, deep lobe tumors, inflammatory conditions, minimally invasive procedures
  - Differentiate motor from sensory
  - Maintenance of gentle technique during surgery
  - Prognostic value of postop result
  - Surgeon comfort

Facial Nerve Monitoring

- Survey studies:
  - US: 60% use some or all of the time
  - Higher volume surgeons, residency training
  - UK: 82% use in majority of cases
- Cost: $228-522 (US)
- Efficacy: mixed results for objective benefit
Operative Discussion:
Facial Nerve Management

- General consensus: if you can save the nerve, then preserve it
- Poorly studied – difficult to normalize/ randomize
- Iyer et al (2008) – cutaneous SCC to parotid. Preservation might lead to increased local recurrence, but not survival

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Operative Discussion:
Facial Nerve Management

- Iseli et al, 2008
- Adenoid cystic carcinoma
- Improved local control
- 10-yr improved survival

<table>
<thead>
<tr>
<th>Outcome/Treatment Group</th>
<th>5 Yr</th>
<th>10 Yr</th>
<th>15 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of local control (n = 44)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Facial nerve preserved (%)</td>
<td>78.9</td>
<td>70.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Facial nerve resected (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td>.259</td>
<td>.420</td>
<td>.266</td>
</tr>
</tbody>
</table>
| Observed survival rate (n = 47)
| Facial nerve preserved (%) | 78.1| 46.8| 41.3|
| Facial nerve resected (%) | 83.6| 58.8| 44.1|
Neck Dissection

- Overall incidence of ~15% in salivary gland cancer
- Occult nodal disease
  - Important to identify for proper staging
  - Helps determine adjuvant treatment
- In the setting of N+ disease
  - Improved locoregional control
  - May improve survival


Elective neck management

- Predictors of occult nodes
  - Histology
  - Stage – size of primary
  - Grade
  - Pain
  - Facial nerve involvement
  - Age >54
  - Extraglandular involvement
  - Lymphovascular invasion

Gold, DR et al, Oto Clin North Am, 2005
# High grade histology

Table 1.
Risk of occult disease based on histology of primary tumor

<table>
<thead>
<tr>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>Adenoid cystic</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Acinic cell</td>
</tr>
<tr>
<td>High-grade Mucoepidermoid</td>
<td>Low-grade mucoepidermoid</td>
</tr>
<tr>
<td>Undifferentiated malignant mixed salivary duct carcinoma</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Epidermoid adenoma</td>
<td></td>
</tr>
</tbody>
</table>

Gold, DR et al, Oto Clin North Am, 2005

Table 1. The N0 neck in salivary gland cancer: management strategies over time

<table>
<thead>
<tr>
<th>Study</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardwell (22), 1967</td>
<td>No elective radical neck dissection, dissection of first echelon nodes for all tumors</td>
</tr>
<tr>
<td>Byers (21), 1982</td>
<td>Dissection of first echelon nodes in all tumors</td>
</tr>
<tr>
<td>Spira et al. (25), 1999</td>
<td>Elective neck dissection for anaplastic or squamous carcinoma</td>
</tr>
<tr>
<td>Armstrong et al. (1), 1992</td>
<td>Staging supraglottic neck dissection for other high-grade tumors</td>
</tr>
<tr>
<td>Califano et al. (26), 1993</td>
<td>Elective neck dissection in cases of mucoepidermoid, anaplastic, and squamous cell sarcomas</td>
</tr>
<tr>
<td>Ball et al. (41), 1995</td>
<td>Neck dissection: high-grade tumors with positive jugulodigastric node biopsy (intraoperative frozen section)</td>
</tr>
<tr>
<td>Frankenthaler et al. (22), 1993</td>
<td>No elective neck dissection, elective postoperative neck irradiation for high-risk tumors</td>
</tr>
<tr>
<td>Kelley and Spro (17), 1996</td>
<td>Elective treatment of the neck for tumors larger than 4 cm or high-grade tumors</td>
</tr>
<tr>
<td>Medina (33), 1998</td>
<td>Intracapsular assessment of level II nodes, if suspicious and frozen section examination reveals metastases: ND Otherwise, elective postoperative neck irradiation if the primary tumor exhibits high-risk clinical-pathological characteristics</td>
</tr>
<tr>
<td>Wang et al. (42), 2012</td>
<td>Comprehensive ND and postoperative radiation: high-risk tumors with adverse features: Upper ND: postoperative radiation; moderate-risk tumors, depending on adverse factors and pT status. Otherwise, low-risk tumors without adverse features</td>
</tr>
<tr>
<td>Herman et al. (27), 2013</td>
<td>T3–T4: Elective neck irradiation if postoperative radiation is indicated preoperatively (based on primary tumor characteristics)</td>
</tr>
<tr>
<td>Norris et al. (26), 2014</td>
<td>Elective neck dissection for all patients</td>
</tr>
</tbody>
</table>

National Cancer Database

- 1998-2012
- Parotid gland cancer
- Captures 70% of cancers in the US
- Excluded squamous cell carcinoma
- N = 22,653

Table 2. Overall Incidence of Nodal and Occult Disease by Histology (in Percentages).

<table>
<thead>
<tr>
<th>Histology</th>
<th>N+</th>
<th>Occult Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>20.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Acinar cell carcinoma</td>
<td>10</td>
<td>4.4</td>
</tr>
<tr>
<td>Adenocarcinoma not otherwise specified</td>
<td>45.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>14.2</td>
<td>7</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic adenoma</td>
<td>23.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Salivary ductal carcinoma</td>
<td>53.5</td>
<td>23.6</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>4.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Basal cell adenocarcinoma</td>
<td>9.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>24.4</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Also depends on T-stage – consistent finding

Age >62 in mucoepidermoid carcinoma

Male gender in univariate analysis
Elective neck management

Fig. 1. Summary of treatment of neck in major salivary gland malignancy.

Other considerations

- Preoperative histology – knowledge is power
- Anticipated need for radiation therapy – knowing the p-staging can be reassuring
- Imaging findings
- Incision planning
- Major/minor gland involvement

Radiotherapy

- No prospective randomized controlled study
- Doses >60Gy more effective
- Not as effective as primary treatment (may have palliative role)
- Appears to be good for local control in adjuvant setting
- Effect on survival
- Favorable retrospective bias
Indications for postop radiation therapy

- Advanced stage tumors (T3/4)
- Invasion into adjacent structures
- Nodal involvement
- High grade histology:
  - High grade MEC, salivary duct, adenoid cystic, squamous, adenocarcinoma
- Perineural invasion
- Recurrent disease
- Positive margin*, tumor spillage

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Fig. 1. Actuarial local control in 198 patients with adenoid cystic carcinoma treated with surgery and postoperative radiotherapy.

Fig. 5. Actuarial survival and freedom from relapse in 198 patients with adenoid cystic carcinoma treated with surgery and postoperative radiotherapy.


SEER analysis of postop radiation therapy

Mahmood U et al, Arch Otolaryngol HN Surg 2011
RTOG 1008

- Is chemotherapy along with radiation beneficial in the adjuvant setting?

<table>
<thead>
<tr>
<th>Histology</th>
<th>Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>S 1. Intermediate-grade adenocarcinoma</td>
<td>R</td>
</tr>
<tr>
<td>T or intermediate-grade mucoepidermoid</td>
<td>A</td>
</tr>
<tr>
<td>R carcinoma</td>
<td>N</td>
</tr>
<tr>
<td>A 2. High-grade adenocarcinoma or high-grade</td>
<td>D</td>
</tr>
<tr>
<td>T mucoepidermoid carcinoma or</td>
<td>O</td>
</tr>
<tr>
<td>I salivary duct carcinoma</td>
<td>M</td>
</tr>
<tr>
<td>F 3. High-grade acinic cell carcinoma or</td>
<td>I</td>
</tr>
<tr>
<td>Y high-grade (&gt; 30% solid component) adenoid</td>
<td>Z</td>
</tr>
<tr>
<td>cystic carcinoma</td>
<td>E</td>
</tr>
</tbody>
</table>

Nodal Status
1. N0
2. N1-3

Conclusion

- Many different salivary malignancies
- Surgery is the mainstay of therapy
  - Complete resection when possible
  - Preserve facial nerve
  - Neck management for more aggressive cancers
- Adjuvant radiation works for locoregional control
  - Unclear if affects survival
  - Benefit of chemo is unclear
The UCSF H&N Surgery Team

Thank you for your attention