H&N Grand Rounds
December 2, 2011

Unusual Salivary Neoplasms
Presentation, Diagnosis, Management

Presenters
Drs. Dario Kunar, Ray Blanco, Carole Fakhry

Discussants
Drs. Fred Yegeneh, Marshall Levine, Geoffrey Neuner, James Sciubba
CC: Palatal mass
HPI:
42 year old female with a four-year history of unusual sensation in the mouth. On dental examination one year ago was noted to have an irregularity of hard palate. Upon follow-up examination, the mass was noted to be persistent and was biopsied. She has no other complaints and denies any symptoms.
• Cc:
  • palate mass

• HPI:
  • 42 year old female with a four-year history of unusual sensation in the mouth.
  • On dental examination one year ago was noted to have an irregularity of hard palate.
  • Upon follow-up examination, the mass was noted to be persistent and was biopsied.
  • She has no other complaints and denies any symptoms.
• PMH:
  • Hodgkin’s Lymphoma - chemotherapy 20 years ago
• Medication: none
• NKDA
• SH: 20 py, Etoh: heavy use
Differential Diagnosis

Clinical

- Benign mixed tumor
- Monomorphic adenoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- PLGA
- Metastatic breast carcinoma
Imaging

Dr. Fred Yegeneh
Imaging Summary
Treatment

- Primary therapy is surgical
- Extent of primary therapy is controversial in literature
- Radiation reported, though rarely used
- Long term surveillance
- Local recurrence rate between 17-33%, regional recurrence 9-18%
Pathology
Cytologic Features

• Cuboidal to columnar cells
• Nuclei ovoid to elongated and bland
• Vesicular to stippled chromatin
• Indistinct cell borders
• Rare mitotic figures
Architectural Features

- Non-encapsulated, infiltrative borders
- Highly variable growth patterns
- No evidence of necrosis
- Perineural invasion
Differential Diagnosis

Microscopic

- Adenoid cystic carcinoma
- Benign mixed tumor
- Papillary cystadenocarcinoma
- Polymorphous low grade adenocarcinoma
Diagnosis

Polymorphous Low Grade Adenocarcinoma
(Terminal Duct Carcinoma
Lobular Carcinoma)
PLGA
Clinical Features

• Wide age range: 21 - 94 years
• Gender predilection: 2:1 female
• Location: near minor gland exclusively
• Asymptomatic, slow growth rate
• Wide range of duration
PLGA

Location

- Great majority are intraoral
  - palate > buccal > tongue base > upper lip
<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Cases</th>
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<tbody>
<tr>
<td>Palate</td>
<td>24</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>5</td>
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<tr>
<td>Base of tongue</td>
<td>3</td>
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<tr>
<td>Upper inner lip</td>
<td>3</td>
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<tr>
<td>Maxillary MB sulcus</td>
<td>2</td>
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<tr>
<td>Mandibular area</td>
<td>2</td>
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<tr>
<td>Lateral tongue</td>
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</tbody>
</table>

PLGA
Papillary Subtype / Predominant

- More than focal papillary growth
- 2 distinct cell layers
- Uniform nuclei
  - >bland, small to medium
- Cytoplasm with pale to clear quality
- Stroma: mucoid to hyaline
- Thickened basement membrane +/-
Varied histopathology
Malignant but indolent behavior

- Papillary and non-papillary variants
  - ? papillary type more aggressive ?
“PLGA includes papillary growth within its spectrum. Papillary areas of more than focal extent were associated with cervical lymph node metastasis to a statistically significant degree, but this was not true of local recurrence, uncontrolled local recurrence, distant metastasis, or death with tumor.”

PLGA
Treatment & Prognosis

- Conservative, wide local excision
- 17% - 33% recurrence rate
- 15% with regional metastases
- 7.5% with distant metastases
Mr. WG is an 87 year-old man with a seven year history of a mass involving the right parotid gland. There was no sign of facial nerve weakness.

A FNA was done with the report stating “suggestive of mucoepidermoid carcinoma vs a Warthin’s tumor”.

History

- 83 y.o. male with a right parotid mass
- 5 years
- Rx’ed periodically with abx & lemon drops
- This summer became painful and swollen
- Started on Abx, sent for CT scan
- Slight response to Abx
- Referred to me
Past Medical History

- 40 year smoker, no EtOH
- CAD with MI, s/p bypass, aortic valve repair, pacemaker
- HTN
- Hypercholesterolemia
- Back surgery
- T & A
- Appendectomy
Medications

- Coumadin
- Lipitor
- Toprol
- Zetia
- ASA
- Allergic to PCN
Physical Exam

- 4 cm solid parotid mass
- Tender
- Poor mobility
- No ductal discharge
- Facial nerve intact
- No cervical nodes
FNA

- Inconclusive
- Clusters of vacuolated glandular cells, histiocytes, oncocytes and degenerated cystic background
- Warthin’s versus cystic mucoepidermoid carcinoma
Imaging

Fred Yegeneh, M.D.
Imaging Summary
Plan

- Total Parotidectomy
- Frozen section
- Neck dissection based on frozen
Pathology
Histology

Summary

• Nests of large epithelial cells
  • Central areas of necrosis (comedonecrosis)
  • Micropapillary, cribriform, solid, cystic patterns
  • Ductal structures with “Roman bridge” pattern
  • Infiltrative nests and cords into abnormal stroma
  • Large, hyperchromatic, pleomorphic nuclei; increased mitoses; eosinophilic cytoplasm
Histology
Summary

- Stromal features
  - Spindle-shaped and pleomorphic infiltrates
  - Mitotic activity
  - Heterologous foci
    - Chondroid; osteoid
  - Considerable, widespread necrosis
Differential Diagnosis

Histologic

- Adenoid cystic carcinoma
- Mucoepidermoid carcinoma-high grade
- Acinic cell carcinoma
- Cribriform cystadenocarcinoma (LG SDC)
- Papillary cystadenocarcinoma
- Metastatic: prostate adenocarcinoma; mammary adenocarcinoma
Diagnosis

Carcinosarcoma
(Malignant Mixed Tumor)
Carcinosarcoma

Facts

• Uncommon; men > women; high grade; excretory duct origin; rapid growth features
• Most arise de novo - may derive from a long-standing ca ex PA
• Resembles breast ductal carcinoma
• Generally poorly circumscribed
Carcinosarcoma

Facts II

• Variants and subsets
  • Sarcomatoid
  • Micropapillary
    • More aggressive vs “typical” SDCa
  • Mucin-rich
  • Osteoclast-like giant cell
Carcinosarcoma
Tx / Prognosis

- Radical resection
  - Neck dx
- Postoperative RTx
- Behavior / Prognosis
  - 1/3\textsuperscript{rd} with recurrent disease
  - Lymphatic / hematogenous spread
  - 50\% with distant metastases (lung, bone, brain)
  - 60\% to 80\% mortality rates @ 5 years
  - May overexpress HER-2/neu
    - An adverse prognosticator
    - Herceptin a postop tx option
Radiotherapy for Salivary Gland Tumors

Dr. Geoffrey Neuner
Problems with Treating Salivary Gland Cancers

- Not well-studied
- Slow-growing (implications for radiation dose)
- Variety of clinical behaviors
- Occur where likelihood of morbidity from radiotherapy may be high
Slow Growing
(More susceptible to damage from densely ionizing radiation)
Neutrons? Not anymore

Despite increased LC, chronic complications are higher and survival is the same. Neutrons have largely been abandoned.

Table 2. Locoregional control after primary radiotherapy for salivary gland cancer

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Locoregional control (%)</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>Laramore et al. (10)</td>
<td>Photons</td>
<td>12</td>
<td>10 y: 17</td>
<td>Randomized, significant, survival equal</td>
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<tr>
<td></td>
<td>Neutrons</td>
<td>13</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Huber et al. (12)</td>
<td>Photons</td>
<td>21</td>
<td>5 y: 32</td>
<td>Nonrandomized, significant, survival equal</td>
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<td></td>
<td>Mixed beam</td>
<td>25</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrons</td>
<td>29</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Douglas et al. (11)</td>
<td>Neutrons</td>
<td>279</td>
<td>6 y: 59</td>
<td>Mixed, primary RT and gross residual disease</td>
</tr>
<tr>
<td>Wang and Goodman (13)</td>
<td>Photons (twice daily, 65-70 Gy)</td>
<td>24</td>
<td>5 y: 85</td>
<td>5/24 had T1-T2; short follow-up</td>
</tr>
<tr>
<td>Terhaard et al. (4)</td>
<td>Photons (28–74 Gy)</td>
<td>40</td>
<td>5 y: ≤66 Gy: 0 &gt;66 Gy: 50</td>
<td>18% had Stage M1; significant</td>
</tr>
<tr>
<td>Chen et al. (5)</td>
<td>Photons (57–74 Gy)</td>
<td>45</td>
<td>5 y: 70</td>
<td>42% had T1-T2, all N0; &gt;66 Gy: significant better ≤66 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 y: 57</td>
<td></td>
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</table>

Abbreviation: RT = radiotherapy.

Terhaard et al., IJROBP, 2007
Estimating Risk of Occult LN Metastases

<table>
<thead>
<tr>
<th>Total score (T stage plus histologic type)</th>
<th>Parotid gland (%)</th>
<th>Submandibular gland</th>
<th>Oral cavity</th>
<th>Other locations</th>
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<tr>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
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<td>5</td>
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<td>60</td>
<td>—</td>
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<tr>
<td>6</td>
<td>38</td>
<td>50</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

Scale: T1 = 1; T2 = 2; T3-T4 = 3; acinic or adenoid cystic carcinoma or carcinoma ex pleomorphic adenoma = 1; mucoepidermoid = 2; squamous cell or undifferentiated = 3.

From Terhaard et al. (4).

Terhaard et al., IJROBP, 2007
Radiation dose

No significant dose–response relationship has been shown in most studies. However, the total dose is generally adjusted to the resection margin status (4). A trend toward greater local control has been observed for a dose of \( \geq 60 \) Gy (9). For high-risk patients (incomplete resection), a dose of \( \geq 65 \) Gy, and for gross residual disease a dose of 70 Gy, is recommended (4). The general guidelines in head-and-neck oncology for the elective and curative dose to the neck nodes are also applicable to tumors of the salivary glands.
### MDA Dose-Finding Trial (1.8 Gy fractions)

#### Table 6. 2-year actuarial control rates at the primary site and neck by dose

<table>
<thead>
<tr>
<th>Risk</th>
<th>Dose (Gy)</th>
<th>No. pts.</th>
<th>Control rate</th>
<th>No. pts.</th>
<th>Control rate</th>
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<tbody>
<tr>
<td>Lower</td>
<td>≤ 54.0</td>
<td>17</td>
<td>63&lt;sup&gt;1&lt;/sup&gt;</td>
<td>9</td>
<td>89</td>
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<tr>
<td></td>
<td>57.6</td>
<td>66</td>
<td>92&lt;sup&gt;2&lt;/sup&gt;</td>
<td>65</td>
<td>86</td>
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<tr>
<td></td>
<td>63.0</td>
<td>51</td>
<td>89</td>
<td>54</td>
<td>89</td>
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<tr>
<td>Higher</td>
<td>63.0</td>
<td>51</td>
<td>89</td>
<td>61</td>
<td>84</td>
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<td></td>
<td>68.4</td>
<td>54</td>
<td>81</td>
<td>51</td>
<td>77</td>
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</table>

1 vs. 2 \( p = 2.34 \)

Only Data – From Uterine Sarcoma EORTC Trial

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<th></th>
<th>Radiotherapy (n = 46)</th>
<th>Observation (n = 45)</th>
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<tr>
<td>No local recurrence</td>
<td>28 (61%)</td>
<td>21 (47%)</td>
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<tr>
<td>Local recurrence only</td>
<td>2 (4%)</td>
<td>11 (24%)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>7 (15%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Local followed by distant</td>
<td>1 (2%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Distant followed by local</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Simultaneous local and distant</td>
<td>6 (13%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Any local recurrence</td>
<td>11 (24%)</td>
<td>21 (47%)</td>
</tr>
<tr>
<td>Any distant metastases</td>
<td>16 (35%)</td>
<td>13 (29%)</td>
</tr>
</tbody>
</table>
Pt. W.G.

• Pathological findings
  • LNs negative (don’t have to cover neck)
  • Margins negative (though close at 0.1mm) – intermediate risk dose (60-65 Gy)
### Radiation Therapy Plan Evaluation

<table>
<thead>
<tr>
<th>VMAT Line</th>
<th>Structure</th>
<th>Approval Status</th>
<th>Plan</th>
<th>Course</th>
<th>Volume [cm³]</th>
<th>Dose Cover [%]</th>
<th>Sampling Cover [%]</th>
<th>Min Dose [cGy]</th>
<th>Max Dose [cGy]</th>
<th>Mean Dose [cGy]</th>
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<td>1</td>
<td>BODY</td>
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<td>Plan Sum-3FLD</td>
<td>C1</td>
<td>11.2</td>
<td>100.0</td>
<td>89.9</td>
<td>487.3</td>
<td>1907.2</td>
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<td>1.1</td>
<td>100.0</td>
<td>98.8</td>
<td>286.7</td>
<td>387.8</td>
<td>346.3</td>
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<td>100.0</td>
<td>1272.2</td>
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<td>13.5</td>
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<td>231.8</td>
<td>221.4</td>
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<td>35.3</td>
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<td>100.2</td>
<td>5964.5</td>
<td>7068.3</td>
<td>6795.9</td>
</tr>
</tbody>
</table>

Some structures are unapproved or rejected.
Case History
Dr. Ray Blanco

• CC is a 60 year-old male with a chief complaint of a right parotid mass that has progressively enlarged over the past 12 months. There was no facial nerve weakness. An earlier biopsy (FNA) of the mass was interpreted as a low grade mucoepidermoid carcinoma.
CC

- PMH: smoker-15 pack year history
- SH: lives alone
- PE:
  - Obesity (300 lbs)
  - Neck examination negative
Imaging

Fred Yeganeh, M.D.
Imaging Summary
Surgical Plan
Dr. Ray Blanco

- Total parotidectomy
- Partial auriculectomy
- Possible facial nerve resection
  - Facial nerve graft
- Frozen section
- Neck dissection
- Plastic surgery consultation for recon.
- Postoperative radiation therapy
Pathology
Nodal Pathology
Histopathology
Nodal Pathology

- 17/34 nodes with metastatic carcinoma
- Multiple lymph node groups involved with tumor
- Extracapsular extension in several node groups
Adenoid Cystic Carcinoma

General Comments

• Characteristics:
  • Slow-growing; widely infiltrative; perineural spread; often present with pain and a mass
  • With palatal presentation, ulceration often
  • Most common intraoral SG tumor overall; in US, MECa, PLGA more frequently noted
  • Combined frequency: minor gland cases more common than major salivary gland cases
Adenoid Cystic Carcinoma
Upper AEDT Distribution

- Site
  - Parotid Gland
  - Palate
  - Submand Gland
  - SN, Nasopharynx
  - Tongue, fom
  - Site, NOS
  - Other named sites

- Number of Cases (%)
  - 336 (21)
  - 271 (17)
  - 210 (13)
  - 184 (11)
  - 129 (8)
  - 242 (15)
  - 173 (14)

Adenoid Cystic Carcinoma

Classic Patterns

- Cribiform - most common
- Tubular
- Solid (when more than 30%) - least common

- Cell components: ductal / myoepithelial
  - Generally bland cytology
Adenoid Cystic Carcinoma  
**Dedifferentiated Variant**

- Mitotic figures present
- Comedonecrosis noted in solid areas
- An adenocarcinoma or undifferentiated carcinoma develops in general
- Ki-67 proliferation indices elevated in dedifferentiated foci
- Clinical course: rapid progression, frequent recurrence, metastasis
Post-Surgical Management

Dr. Geoffrey Neuner
Dr. Marshall Levine
Pt. C.C.

- Adenoid Cystic Carcinoma – What do we use from pathology to decide dose?
  - Positive Margin – as it was extensively involved, dose to resection bed would be essentially full dose (70 Gy).
  - Lymph Nodes (17/34, some with ECE) – Dose is dictated by concern for microscopic residual disease. Intermediate risk dose in radiation oncology is ~ 60 Gy.
  - Chemotherapy given because of high risk and some retrospective data to support its use.
• Critical Structures – Have to use reasonable assumptions for planning system to yield a plan that does is not inadequate.
• Radiation dose effects are grouped into two types:
  • Stochastic – dose independent for severity, dose dependent for likelihood, no threshold dose (majority of structures)
  • Deterministic – dose dependent for severity, threshold dose exists (radiation cataract in the lens 5 Gy)
Salivary Gland Carcinomas and Chemotherapy

Marshall A. Levine
How to Utilize Chemotherapy for Salivary Cancer

• Neoadjuvant chemotherapy: large, bulky unresectable masses, requires activity of chemotherapy agents against the tumor
• Adjuvant chemotherapy: resected tumor, requires activity of chemotherapy agents against the tumor
• Concurrent chemoradiotherapy: sensitizing agent to make radiation more effective
Effectiveness of Chemotherapy
Salivary Gland Carcinoma

• Most chemotherapy agents lack activity against salivary gland carcinomas
• Agents tested:
  Paclitaxel: Gilbert, Head & Neck: 2006: 197-204
  ECOG 1394: mucoepidermoid, adenocarcinoma:
    31 patients, 26% partial responses
  adenoid cystic: none of fourteen patients
  high dose chosen = 200mg/m2
  Cisplatin: Licitra, Cancer 1991;68:1874-1877,
    18%, 5-9 month response
    20%, 6 months
  Vinorelbine + Doxorubicin: Airoldi,Cancer 2001; 91:541-547, 44%
Other Agents Evaluated

- Bortezimib + doxorubicin: ineffective
- Trastuzumab (Herceptin): ineffective
- Lapatinib: inhibits EGFR and Her-2/neu; under investigation
“Ancient History” of Standard Chemotherapy Agents for Salivary Carcinoma

- Posner, Ervin, et al., Cancer 1982;50:2261-2264; Trial of AC and PBM at DFCI for a variety of salivary gland carcinomas including adenoid cystic, acinic cell, mucoepidermoid, and adenocarcinoma: only 13 patients were in this series. The series was small, the chemotherapy was given at different times in the therapeutic plan, and the results were inconsistent and variable.
Concurrent Chemoradiotherapy for Adenoid Cystic Carcinoma

  Organ sparing definitive primary therapy 2000-2004
  Only five patients who were either unresectable or desired organ preservation
  Carboplatin-paclitaxel
  All patients responded with median F/U 36 months, duration of 20-43 months
Adjuvant Chemotherapy for Salivary Gland

- Schoenfeld, Sher, (DFCI) Int.J.Radiation Oncology Biol Phys 2010; 1-7
- 35 patients
- 2005-2010
- Histologic types: adenoid cystic 15, mucoepidermoid 6, adenocarcinoma 3, acinic cell 3, others 8
- Sites of primary: parotid 17, submandibular 6, tongue 4, palate 4, others 4
- Radiation median 66cGy; chemoradiotherapy 22pts
Most common chemo regimen: carbo-paclitaxel

CRT patients had poorer prognoses than XRT due to primary T stage (T3-4 = 55 vs 31 %), node involvement (36 vs 8%), and positive margins (59 vs 38%)

Local control 92%

Distal metastases 14%

Grade 3 mucositis more common in CRT (86 vs 30%)

Grade 4 toxicity: none
H. Lee Moffitt Experience for Postoperative CRT for Salivary Gland Carcinoma

- Retrospective series 1998-2007
- Matched CRT patients with XRT alone patients
- Median PFS: CRT 53 vs 40 months
- One year PFS: CRT 83 vs 69%
- Three year PFS: CRT 53 vs 54%
- Median local PFS: CRT 53 vs 21%
- Prognosis poorer for higher T stage, facial nerve palsy, higher tumor grade, positive or close margins, or older age.
- This was a small retrospective study with limited follow-up