ARRO Case: Salivary Gland Cancer

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Case Presentation

- 66 y.o. female presents with a painless mass under left chin that had been slowly enlarging for approximately 5 years
- ROS negative for weight loss, trismus, dysphagia, odynopagia
Case Presentation

• Pertinent physical exam findings:
  – Head and Face: no craniofacial deformities, no scars, lesions or masses
  – Neck: **Firm, fixed, non-tender left submental mass.** No other palpable LAD, No thyromegaly
CT Findings

4.8 cm x 2.6 cm x 6.0 cm sublingual mass with prominent enhancement surrounding a relatively centrally, necrotic area. No lymphadenopathy
Surgical Management

• Patient underwent excision of left sublingual mass and left submandibular gland and left level 1A and 1B dissection
  – Intraoperative findings: Normal appearing submandibular gland with approximately 4 cm sublingual mass separate from submandibular gland
Pathology

- Left sublingual gland: carcinoma ex pleomorphic adenoma
  - intermediate grade with areas of extension up to the resection margin
  - no extraparenchymal extension
  - 5.5cm x 5.0cm x 2.5cm

- Left submandibular gland: negative for tumor
- Left level 1A: 2 lymph nodes negative for tumor
- Left facial nodes: 3 lymph nodes negative for tumor

→ pT3N0
Simulation and Planning

- Thermoplastic head and shoulder mask
- Bite block and tongue blade
  - Lips protrude
  - Minimizes toxicity to palate (minor salivary glands)
Radiation Treatment Plan

- Preoperative CT scan fused with planning CT to generate preoperative GTV

- **PTV 1**: 66 Gy in 33 fractions (2.0 Gy/Fx)
  - 66 Gy used due to positive margins

- **PTV 2**: 59.4 Gy in 33 fractions (1.8 Gy/Fx)
  - Left levels Ib-IV nodes treated

- **PTV 3**: 56.1 Gy in 33 fractions (1.7 Gy/Fx)
  - Contralateral levels Ib-III electively treated due proximity of tumor to midline

- PTVs subtracted from skin-3mm
Treatment Planning

• Plan generated using volumetric modulated arc therapy (VMAT) with 6 MV beams
Dose Distribution
Dose Distribution
# Dose Constraints (Standard Fractionation)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Volume/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>Max &lt; 54 Gy</td>
</tr>
<tr>
<td></td>
<td>1 cc &lt; 60 Gy</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Max &lt; 45 Gy</td>
</tr>
<tr>
<td></td>
<td>0.03 cc &lt; 48 Gy</td>
</tr>
<tr>
<td>Mandible</td>
<td>Max &lt; 70 Gy</td>
</tr>
<tr>
<td></td>
<td>1 cc &lt; 70 Gy</td>
</tr>
<tr>
<td>TMJ</td>
<td>Max &lt; 40 Gy</td>
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<tr>
<td></td>
<td>V50 &lt; 100%</td>
</tr>
<tr>
<td></td>
<td>V65 &lt; 1 cc</td>
</tr>
<tr>
<td>Oral Cavity, Lips</td>
<td>Mean &lt; 30 Gy</td>
</tr>
<tr>
<td>Parotid</td>
<td>Mean &lt; 26 Gy</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral V30 &lt; 50%</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>Mean &lt; 45 Gy</td>
</tr>
<tr>
<td></td>
<td>Uninvolved &lt; 39 Gy</td>
</tr>
</tbody>
</table>
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(Standard Fractionation)

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<tr>
<th>Structure</th>
<th>Volume/dose</th>
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</thead>
<tbody>
<tr>
<td>Optic Chiasm</td>
<td>Max &lt; 55Gy</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Max &lt; 55Gy</td>
</tr>
<tr>
<td>Eye</td>
<td>Max &lt; 50 Gy&lt;br&gt;Mean &lt; 35 Gy</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>Mean &lt; 30 Gy</td>
</tr>
<tr>
<td>Lens</td>
<td>Mean &lt; 5-10 Gy&lt;br&gt;Max &lt; 25 Gy</td>
</tr>
<tr>
<td>Cochlea</td>
<td>Mean &lt; 30 Gy</td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>Max &lt; 66 Gy</td>
</tr>
<tr>
<td>Constrictors</td>
<td>Mean &lt; 45 Gy</td>
</tr>
</tbody>
</table>
Dose Volume Histogram
Introduction

• Salivary gland tumors can arise in the three major paired salivary glands (parotid, submandibular, and sublingual) or in the minor salivary glands located throughout the upper aerodigestive tract
• Around 50% of minor salivary glands are located in the hard palate

\(^1\)
Etiology

• The causes of salivary gland tumors (SGTs) have not been clearly established.
• Shown to be associated with nutritional deficiencies, exposure to ionizing radiation, ultraviolet exposure, Epstein-Barr virus, hair dye, and other occupational exposures\(^2\).
Epidemiology

• Account for 3% to 5% of all head and neck cancers

• 70% of tumors arise in parotid (25% malignant)

• 8% arise in submandibular (43% malignant)

• 22% arise in minor salivary glands (65% malignant)
Histology

2005 WHO classification of malignant epithelial SGTs

- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Clear cell carcinoma, NOS
- Basal cell adenocarcinoma
- Malignant sebaceous tumors
- Cystadenocarcinoma
- Low-grade cribriform cystadenocarcinoma
- Mucinous adenocarcinoma
- Oncocytic carcinoma

- Salivary duct carcinoma
- Adenocarcinoma, NOS
- Myoepithelial carcinoma
- Carcinoma ex pleomorphc adenoma
- Carcinosarcoma
- Metastasizing pleomorphic adenoma
- Squamous cell carcinoma
- Small cell carcinoma
- Large cell carcinoma
- Lymphoepithelial carcinoma
- Sialoblastoma
Histology

- Mucoepidermoid carcinoma is the most common malignant histology of parotid gland

- Adenoid cystic carcinoma is the most common malignant histology of the submandibular and minor salivary glands

- Squamous cell carcinomas in the parotid region usually represent lymph node metastases from cutaneous squamous cell carcinomas rather than primary gland carcinomas
Histology

• Adenoid cystic carcinoma is usually low grade but has often associated with PNI and distant metastases are common

• Carcinoma ex pleomorphic adenoma (this case) is a carcinomatous transformation within a primary or recurrent pleomorphic adenoma.
  – Rate of malignant transformation may be as high as 25%³
  – Histologic features include capsule invasion, hemorrhage, and necrosis alternating with areas presenting classical features of pleomorphic adenoma⁴
Clinical Presentation

- Most patients with SGT are asymptomatic and present with a solitary, painless mass
  - Symptoms are related to region which tumor originates
- Low-grade SGTs are slow growing and rarely invade local anatomic structures
- One third of parotid tumors may have facial nerve involvement
Clinical Presentation

• The risk of nodal involvement is based on a combination of T stage, tumor location (primary site involving the pharynx), and histology
  – The highest risk of nodal involvement is with squamous cell, undifferentiated, and salivary duct cancers
  – Propensity for nodal involvement: minor salivary glands > submandibular/sublingual glands > parotid glands
Anatomy

**Parotid**
- superficial to and partly posterior to mandibular ramus
- overlaps posterior portion of masseter
- facial nerve enters deep surface as a single trunk
- superficial and deep lobe separated by facial nerve

**Submandibular gland**
- located between anterior and posterior bellies of digastric and lower mandible

**Sublingual gland**
- located between floor of mouth, mandible, mylohyoid, and genioglossus
Work Up and Staging

• Work up includes H&P, labs, CT, and MRI
• Physical exam should include full oral cavity inspection and bimanual palpation of areas suspicious for involvement
  • Minor salivary gland tumors usually present as a submucosal mass
• Fine needle aspiration or ultrasound-guided core needle biopsy of suspicious lesion
  • FNA is preferred for tumor of the parotid gland to minimize risk of tumor seeding and injury to facial nerve
Imaging

• CT used to evaluate nodal metastases and bony destruction
• MRI can be used to determine soft-tumor infiltration, delineation of PNI, and can be used to evaluate for intracranial spread
AJCC 8\textsuperscript{th} edition\textsuperscript{4}

- Summary of changes
  - Separate N category for patients treated without cervical LN dissection (clinical N) and with cervical LN dissection (pathologic N)
  - Clinically overt ENE(+)→cN3b
  - Pathologic presence of ENE is designated pN2a for single ipsilateral node <3cm and pN3b for all other node(s)
Tumor

T1: ≤2 cm without extraparenchymal extension
T2: >2 cm but <4 cm without extraparenchymal extension
T3: >4 cm and/or extraparenchymal extension
T4a: invades skin, mandible, ear canal, and/or facial nerve
T4b: invades skull base, and/or pterygoid plates and/or encases carotid artery

Clinical N (cN)

N0: No regional LNs
N1: single ipsilateral LN <3 cm, ENE(-)
N2a: single ipsilateral LN >3 and <6 cm, ENE(-)
N2b: multiple ipsilateral LNs, <6 cm, ENE(-)
N2c: bilateral or contralateral LNs, <6 cm, ENE(-)
N3a: LN >6 cm and ENE(-)
N3b: single ipsilateral LN >3 cm, ENE(+) or multiple ipsilateral, contralateral, or bilateral LNs any with ENE(+) or a single contralateral LN <3 cm with ENE(+) or ENE(+)

Pathologic N (pN)

N0: No regional LNs
N1: single ipsilateral LN <3 cm, ENE(-)
N2a: single ipsilateral LN <3 cm, ENE(+) or single ipsilateral LN >3 and <6 cm, ENE(-)
N2b: multiple ipsilateral LNs, <6 cm, ENE(-)
N2c: bilateral or contralateral LNs, <6 cm, ENE(-)
N3a: LN >6 cm and ENE(-)
N3b: single ipsilateral LN >3 cm, ENE(+) or multiple ipsilateral, contralateral, or bilateral LNs any with ENE(+) or a single contralateral LN <3 cm with ENE(+) or ENE(+)

Distant Metastases

M0: no distant metastases
M1: distant metastases
Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0</td>
</tr>
<tr>
<td>II</td>
<td>T2N0</td>
</tr>
<tr>
<td>III</td>
<td>T3N0 or T1-2N1</td>
</tr>
<tr>
<td>IVA</td>
<td>T4a or N2</td>
</tr>
<tr>
<td>IVB</td>
<td>T4b or N3</td>
</tr>
<tr>
<td>IVC</td>
<td>M1</td>
</tr>
</tbody>
</table>
Treatment Paradigm

Surgical Resection +/- adjuvant treatment based on presence of adverse features
Surgery

• Adequate resection is primary treatment for SGTs
• Tumors of the parotid are most often located in the superficial lobe
  • The facial nerve can be preserved if functioning preoperatively\(^6\)
  • Preoperative involvement with facial nerve palsy or direct invasion requires facial nerve sacrifice
  • Malignant deep lobe parotid tumors are less common
Adjuvant Radiation

- No prospective trials randomizing to postoperative radiation
- Single-institution series have demonstrated improved survival with adjuvant radiation
## Selected Postoperative Series

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
</table>
| MSKCC\(^7\) | 98 | **5-yr LC:**  
Stage I/II 79% → 91%  
Stage III/IV 17% → 51% (p=0.14)  
**5-yr OS:**  
Stage I/II 96% → 82%  
Stage III/IV 9.5 → 51% (p=0.015)  
**N+** 19% → 49% (p=0.015) | RT indicated for stage III/IV and positive LNs |
| John Hopkins\(^8\) | 87 | **5 yr LC**  
58% → 92% (p=0.001)  
**5-yr OS**  
59% → 75% (p=0.01) | Facial nerve paresis, undifferentiated histology, male sex, skin invasion, and no adjuvant RT associated with worse outcomes |
| NWHHT\(^9\) | 538 | **10 yr LC**  
T(3-4) 18% → 84%  
Close margins 55% → 95%  
Incomplete resection 44% → 82%  
Bone invasion 54% → 86%  
PNI 60% → 88% | Postoperative RT (at least 60 Gy) for T(3-4) tumors, close/+margins, bone invasion, PNI, and pN+ |
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| UCSF\(^{10}\) | 63 patients (carcinoma ex-pleomorphic adenoma) | **5-yr LC** 49%→75% (p = 0.005)  
**5-yr OS** (N0 or Nx) 52%→71% (p=0.01) | Surgery + postoperative RT should be standard of care for carcinoma ex-pleomorphic adenoma  
Survival decrement with adjuvant RT attributed to worse disease characteristics in radiation group. Subset with negative lymph nodes or unknown had a benefit |
Adverse Features

Indications for postoperative radiation include:
- Positive/close margins
- T3/T4 tumor
- pN+ disease
- High-grade histology
- Extraglandular extension
- Bone invasion
- LVSI
- PNI
Radiation Treatment

• 60 Gy to the postoperative bed

• 66 Gy may be used for close/positive margins

• IMRT may allow for sparing of mandible, cochlea, spinal cord, and oropharynx
Radiation Treatment

Parotid Gland

- CTV individualized based on disease extent and surgery
- Parapharyngeal space and infratemporal fossa should be covered
- In tumors with named perineural invasion, cranial nerve should be treated to the base of skull
  - Always cover CNVII to stylomastoid foramen for parotid tumor
  - For gross involvement of CNVII, cover petrous bone and formen ovale (due to connections with CNV3)\(^{11}\)
Radiation Treatment

Parapharyngeal space

Stylomastoid foramen
Radiation Treatment

Submandibular Gland

- Similar to parotid gland, CTV based on initial tumor involvement extent of resection
Radiation Treatment

Minor salivary glands

- For tumors of the palate or paranasal sinuses, the base of skull is included because of its proximity to the tumor bed.
- Indications for neck radiation for minor salivary gland tumor are primary from tongue, floor of mouth, pharynx, or larynx, no neck dissection, or N+ neck.
Radiation Treatment: Elective radiation of neck nodes

- Postoperative radiotherapy to the \( N_0 \) neck is based on T stage, histologic subtype, and location.
- Elective treatment of the neck is indicated for almost all submandibular glands (except for T1 acinic or T1 adenoid cystic tumors).
- A dose of at least 46 Gy is recommended to levels I-III.
- Radiation to the N+ neck results in improved local control.
- For the N+ neck, levels I-V should be treated with a dose of at least 60 Gy for the level with positive nodes.
Definitive Radiation

• Unresectable SGTs can be treated to at 66-70 Gy

• Local control rates have reported to be between 20-30%\textsuperscript{12,13}
Neutron Therapy

- RTOG-MRC randomized to neutrons (17-22 nGy) vs. photon/electrons (55 Gy/4 weeks or 70 Gy/7.5 weeks)$^{14}$
  - 10-year LRC neutrons 56% vs. photons/electrons 17% (SS)
  - OS 25% vs. 15% (NS)
- Results in high locoregional control but no difference in survival. Concern for high rates of late toxicity
- May be used for unresectable, residual, or recurrent salivary gland tumors
- University of Washington retrospective series showed increase in CSS for stage I-II disease, lack of skull base invasion, and minor salivary gland site$^{15}$
Systemic Therapy

• No level I evidence to demonstrate benefit of addition of chemotherapy
Ongoing trial: RTOG 1008

- **RTOG 1008: A Randomized Phase II/Phase III Study of Adjuvant Concurrent Radiation and Chemotherapy versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors**
  
  - **Inclusion Criteria:**
    - Salivary gland carcinomas involving major or minor salivary glands
    - Intermediate-grade or high-grade Adenocarcinoma or mucoepidermoid carcinoma
    - High-grade acinic cell or adenoid cystic carcinoma
    - Curative intent surgical resection and found to have: T3-4, or N1-3, or T1-2N0 patients with positive or close (≤1mm) margins
RTOG 1008

- **Arm 1**: Radiation 60-66Gy in 2Gy daily fractions with concurrent cisplatin 40mg/m^2 weekly during radiation for 7 cycles

- **Arm 2**: Radiation alone 60-66Gy in 2Gy daily fractions
Treatment Sequelae

- Xerostomia
- Trismus
- Chronic otitis media/externa
- Hearing loss
Post-treatment Follow-Up

H&P
- Year 1, every 1-3 months
- Year 2 every 2-6 months
- Years 3-5, every 4-8 months
- >5 years, annually
Summary

• Malignant SGTs are a diverse group with various anatomic locations and histologic subtypes
• Surgery is mainstay of treatment. Adjuvant radiation is indicated when adverse features are present
• Treatment volumes may depend on initial location of tumor, histology, and pathologic features
• RTOG 1008 is investigating the use of adjuvant chemotherapy