Salivary Gland Tumors
An Update

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Objectives

Build on previous ARROCases for salivary gland tumors (SGTs) including benign & malignant disease:

1. Recognize the presentation of pleomorphic adenoma (PA) and carcinoma ex PA (CaXPA)
2. Develop a framework for managing benign & malignant SGTs
3. Understand the epidemiology, classification, & prognosis
4. Review relevant clinical trials
A lump in the neck

• 40-year-old aesthetician with a slowly growing mass in her neck over 3-4 months

• No pain, trismus, facial weakness, numbness, dysphagia, or odynophagia

• Physical exam with focus on the head & neck (H&N):
  – A 3cm, firm, nontender, mobile mass at the angle of the mandible
  – No other palpable masses or adenopathy
  – Cranial nerve exam is normal
  – Oral mucosa & skin are intact
Referred to ENT

- Ultrasound shows a single hypoechoic mass in the parotid with posterior acoustic enhancement
- Fine Needle Aspiration & Biopsy (FNAB) consistent with pleomorphic adenoma (PA)
- Superficial parotidectomy reveals a tumor in the superficial lobe of the parotid
- Pathology shows PA with a ruptured capsule
- Transient CN VII paralysis with recovery 4 months later
- Discharged to her GP after 5 years of uneventful follow-up
5 Years Later...

- She returns with a 2-year history of a mass in same location at the angle of the mandible
- CT shows an enhancing mass adjacent to the residual deep lobe with necrosis
- FNAB shows **recurrent pleomorphic adenoma**
- Discussed at multidisciplinary cancer conference (MCC)
  - Resectability borderline, but **definitive radiation felt to be inferior to surgery**
- Revision parotidectomy shows **one mass & two nodules** in the **deep parotid remnant**
- Final pathology is **again PA with a close margin**
- Postop MRI shows no residual tumor
- Discussed again at MCC
  - Not a candidate for re-resection and consensus for adjuvant radiation treatment based on **high-risk features for local recurrence**
    - 5000cGy in 20 daily fractions for microscopic residual disease to the tumor bed and surgical scar with a bolus
Approach to a lump in the neck

- **Congenital**
  - Usually seen in children

- **Infectious/Inflammatory**
  - Infectious: viral, bacterial, parasitic
  - Noninflx: stone, sarcoid, Castleman, Kawasaki

- **Neoplastic** (benign or malignant)
  - Primary (Salivary, thyroid, paraganglioma, schwannoma, lymphoma, lipoma/cyst)
  - Mets (aerodigestive or skin)

### Adult with a Neck Mass

- **History & Physical** (Focus on H&N)
  - Congenital or Infectious/Inflammatory
  - Neoplasm
    - CT/MRI (H&N) & FNAB* (+/- Path Review)
    - ENT & Endoscopy

*role of FNAB in workup is controversial, but often recommended because it can change management in 35% of cases*  

**for a non-neoplastic parotid mass:** SP1TS *Salivary duct stone, Parotitis, 1st brachial cleft cyst, fatty parotid Tail, Sarcoidosis*

@RadOncMnemonics

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ARRO
Salivary Gland Tumors (SGTs) are usually in the parotid

- Uncommon (5.5 per 100,000)
- Benign tumors more common in young females (median age 46)
- Malignant tumors more common in older men (median age 54)

**Rule of thumb:** as the size of the gland decreases the incidence of malignancy increases (25/50/75% for Parotid/Submandibular/Sublingual or minor)

- **Parotid:** 70-85% of all tumors & 25-32% are malignant
- **Minor Glands:** 22% of all tumors & 45-82% are malignant
- **Sublingual:** <1-5% of all tumors & 70-90% are malignant
- **Submandibular Glands:** 8% of all tumors & 37-45% are malignant

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Most SGTs are Pleomorphic Adenomas

- 53-77% of all parotid tumors are Pleomorphic Adenomas (PAs)\(^6\)
- 7-14% are Warthin’s
- <10% Oncocytoma, cystadenoma, & others

Benign parotid tumors are found in 65-75% of patients
PA is one histology of many for SGTs

Histologic classification for salivary gland tumors in the WHO 4th Edition has 22 carcinomas, 11 benign tumors, 4 non-neoplastic epithelial lesions, 3 benign soft-tissue entities, and MALT Lymphoma, making it one of the most extensive classifications for tumors.

<table>
<thead>
<tr>
<th>Malignant tumors</th>
<th>Benign tumors</th>
<th>Non-neoplastic epithelial lesions</th>
<th>Benign soft tissue lesions</th>
<th>Hematolymphoid tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>Secretory carcinoma</td>
<td>Sclerosing polycystic adenosis</td>
<td>Hemangioma</td>
<td>Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>Sebaceous adenocarcinoma</td>
<td>Nodular oncocytic hyperplasia</td>
<td>Lipoma/sialolipoma</td>
<td></td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>Carcinosarcoma</td>
<td>Lymphoepithelial sialadenitis</td>
<td>Nodular fasciitis</td>
<td></td>
</tr>
<tr>
<td>Polymorphous adenocarcinoma</td>
<td>Poorly differentiated carcinoma</td>
<td>Intercalated duct hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>Undifferentiated carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>Large cell neuroendocrine carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td>Small cell neuroendocrine carcinoma</td>
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<tr>
<td>Adenocarcinoma, NOS</td>
<td>Lymphoepithelial carcinoma</td>
<td></td>
<td></td>
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<tr>
<td>Salivary duct carcinoma</td>
<td>Squamous cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td>Oncocytic carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>Uncertain malignant potential</td>
<td></td>
<td></td>
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<tr>
<td>Carcinoma ex pleomorphic adenoma</td>
<td>Sialoblastoma</td>
<td></td>
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</tr>
</tbody>
</table>
SGT histologies having different anatomical origins

- Acinic cell ca
- Basaloid adenoca
- Myoepithelial ca
- Adenoid cystic ca
- Pleomorphic adenoma
- Epithelial-myxoepithelial ca
- Warthin’s Oncocytic ca
- Mucoepidermoid ca
- Salivary duct ca
- Adenocarcinoma

Source: StatPearls
PA often presents as painless swelling

- Painless swelling in 87%
- Advanced disease will have more site-specific symptoms (e.g., facial nerve palsy, trismus, pain, or dysphagia for the parotid)
- FNA has 50-85% sensitivity & 75-99% specificity\(^9\)
PA has an unclear etiology

Relationships to consider asking on history for any suspected SGT

Viral: EBV, HHV-8, HPV$^{11-13}$

Occupational: Hairdresser, mining (asbestos), plumber, automobile manufacturing$^{14}$

Genetic: KIT, MYB-NFIB, PLAG1, ECT1-MAML2, MAD1L1, HMGIC, HER2/neu, RAS, c-fos, Sox, BCL2, TrkC/NTRK3$^{16}$

Ionizing Radiation$^{15}$

The most evidence (for salivary carcinomas) is previous ionizing radiation at a young age or at least 20 years prior
Management of PAs

Management of pleomorphic adenomas is similar to most benign SGTs, with the exception of more evidence for radiation treatment in special situations for PAs.

<table>
<thead>
<tr>
<th>Local Disease</th>
<th>Primary surgical treatment is dependent on location (parotid superficial or deep lobe, submandibular gland, or other gland). <strong>Adjuvant RT is sometimes considered for high-risk features for local recurrence.</strong> <strong>Definitive RT is second-line</strong> for unresectable disease. Observation alone for some benign histologies (e.g. Warthin’s) may be appropriate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>Usually no neck dissection or elective nodal irradiation is indicated.</td>
</tr>
<tr>
<td>Recurrent Disease</td>
<td>Surgery is first-line <strong>and consideration for adjuvant RT including other high-risk features.</strong> If unresectable, <strong>consider definitive RT.</strong></td>
</tr>
</tbody>
</table>
| Follow-up       | In a multidisciplinary clinic with radiation oncologists & H&N surgeons:  
- At least weekly on treatment  
- 2-6 weeks post-treatment for the first follow-up  
- Years 1-2 at least q3 months (CT/MRI at 10-12 weeks post-treatment)  
- Year 3 at least q4 months  
- Years 4-5 at least q6 months  
- Then annually  
Fiber-optic nasopharyngoscopy, speech language pathology for pharyngeal/laryngeal function, dental, audiometry, or ophthalmology assessments as clinically indicated |

Sources: PMH 2019\(^{21}\), Thielker 2018\(^{39}\)
PAs are often treated with surgery alone

- Treatment for PA is similar to that of most benign SGTs with primary treatment being surgery\textsuperscript{17}
- If left untreated, PAs have a risk of malignant transformation
  - 2% at 5 years & 10% at 15 years\textsuperscript{18}
- Parotid surgery with preservation of CNVII has > 95% chance of cure at 10 years,\textsuperscript{18} but facial nerve palsy seen in 5-15% of patients\textsuperscript{18}
- Frey syndrome (sweating & flushing in the preauricular area) seen in up to 62% of patients 6-18 months postop\textsuperscript{18}
- Salivary fistulas and keloids are less common (<5%)\textsuperscript{18}
Parotid PA surgery is limited, but not too limited.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Extent of Surgery</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enucleation</td>
<td>Shelling out of capsular contents</td>
<td>Not appropriate for most SGTs due to high risk of recurrence (20-45%).</td>
</tr>
<tr>
<td>Extracapsular dissection</td>
<td>Removal of tumor with capsule</td>
<td>Technically difficult. Not appropriate for malignant disease.</td>
</tr>
<tr>
<td>Partial superficial parotidectomy</td>
<td>SGT + 1-2cm margin.</td>
<td>Margins may not be achievable.</td>
</tr>
<tr>
<td>Superficial parotidectomy</td>
<td>Superficial lobe</td>
<td>Requires extensive nerve dissection. Less than 5% risk of recurrence.</td>
</tr>
</tbody>
</table>

Historically, enucleation alone was used for pleomorphic adenomas to minimize side effects. This was later found to have high local recurrence rates of 20-45% compared to <5% for superficial parotidectomy and enucleation was abandoned.
Definitive Radiation Treatment for PAs

Unresectable gross benign disease may be considered for radiation treatment alone based on limited retrospective data.

Off Trial: Definitive RT (70Gy in 35 daily fractions) has only ~40% cure rate at 2-5 years so consider intensification\textsuperscript{19,20}

- DAHANCA (70Gy with 6 fractions/wk over 6 wks) or
- HARDWINS (60-66Gy with 10 fractions/wk over 4 wks)
Adjuvant RT for Pleomorphic Adenomas

No mature results from trials. Single-institution series suggest improvements in local control ~10-20% at 10-15 years, especially for high-risk features (e.g. inadequate surgery such as enucleation, positive margins, and multifocal or recurrent disease).\(^{21}\)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>n</th>
<th>Modality</th>
<th>LC (%)</th>
<th>TTF (y)</th>
<th>FU (y)</th>
</tr>
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<tbody>
<tr>
<td>Carew et al. (27)</td>
<td>31</td>
<td>S/SR</td>
<td>94</td>
<td>6.1</td>
<td>7.3*</td>
</tr>
<tr>
<td>Phillips and Olsen (12)</td>
<td>126</td>
<td>S</td>
<td>68</td>
<td>9.9</td>
<td>14.5†</td>
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<tr>
<td>Yugueros et al. (23)</td>
<td>39</td>
<td>S/SR</td>
<td>79</td>
<td>7.5</td>
<td>10.0†</td>
</tr>
<tr>
<td>Douglas et al. (25)</td>
<td>16</td>
<td>SR</td>
<td>85</td>
<td>2.4</td>
<td>6.9*</td>
</tr>
<tr>
<td>Glas et al. (1)</td>
<td>52</td>
<td>S</td>
<td>85</td>
<td>NA</td>
<td>9.0*</td>
</tr>
<tr>
<td>Renehan et al. (26)</td>
<td>114</td>
<td>S/SR</td>
<td>85</td>
<td>6.1</td>
<td>14.0*</td>
</tr>
<tr>
<td>Fee et al. (21)</td>
<td>26</td>
<td>S</td>
<td>65</td>
<td>2.1</td>
<td>NA</td>
</tr>
<tr>
<td>Gleave et al. (8)</td>
<td>42</td>
<td>SR</td>
<td>95</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Niparko et al. (22)</td>
<td>48</td>
<td>S</td>
<td>53</td>
<td>6.0</td>
<td>16.1†</td>
</tr>
<tr>
<td>Dawson (16)</td>
<td>28</td>
<td>SR</td>
<td>79</td>
<td>NA</td>
<td>8.5†</td>
</tr>
<tr>
<td>Leonetti et al. (24)</td>
<td>42</td>
<td>S</td>
<td>83</td>
<td>5.4</td>
<td>7.2†</td>
</tr>
<tr>
<td>Zbaren et al. (13)</td>
<td>33</td>
<td>S</td>
<td>73</td>
<td>8.8</td>
<td>8.3†</td>
</tr>
<tr>
<td>Chen et al. (UCSF)</td>
<td>34</td>
<td>SR</td>
<td>94</td>
<td>3.3</td>
<td>17.4*</td>
</tr>
</tbody>
</table>

Select studies of the treatment for recurrent pleomorphic adenoma

\(n = \) number of patients; 
S = surgery alone; SR = surgery + postop RT; LC = local control; TTF = time to failure; FU = follow-up

* median
† mean
Adjuvant RT indications for PAs

High-Risk Features for Local Recurrence of Pleomorphic Adenoma

<table>
<thead>
<tr>
<th>Univariate analyses</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;42</td>
<td>1</td>
<td></td>
<td>0.471</td>
</tr>
<tr>
<td>≥42</td>
<td>0.624</td>
<td>0.173–2.247</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td>0.354</td>
</tr>
<tr>
<td>Male</td>
<td>1.864</td>
<td>0.500–6.952</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms, yr</td>
<td>0.916</td>
<td>0.768–1.092</td>
<td>0.328</td>
</tr>
<tr>
<td>Size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>1</td>
<td></td>
<td>0.315</td>
</tr>
<tr>
<td>2–4</td>
<td>2.912</td>
<td>0.362–23.402</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>1.790</td>
<td>0.111–28.733</td>
<td>0.681</td>
</tr>
<tr>
<td>Pathological subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular type</td>
<td>Infinite</td>
<td>0.993</td>
<td></td>
</tr>
<tr>
<td>Classic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid type</td>
<td>2.291</td>
<td>0.635–8.264</td>
<td>0.205</td>
</tr>
<tr>
<td>Incomplete capsule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td></td>
<td>0.457</td>
</tr>
<tr>
<td>Present</td>
<td>1.672</td>
<td>0.432–6.473</td>
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</table>

<table>
<thead>
<tr>
<th>Multivariate analyses</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudopodia</td>
<td></td>
<td></td>
<td>0.512</td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1.534</td>
<td>0.427–5.519</td>
<td></td>
</tr>
<tr>
<td>Satellite nodule</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Present</td>
<td>6.782</td>
<td>1.897–24.248</td>
<td></td>
</tr>
<tr>
<td>Resection margin *</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupture</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20.456</td>
<td>4.454–93.947</td>
<td></td>
</tr>
</tbody>
</table>

*when inadequate margins cannot be managed surgically

Also mentioned in the literature as indications are recurrences, especially multiple recurrences, and multifocal disease

Postop radiation is not always used for tumor spill or close margins (up to ~90% cure with no further treatment).

Consider discussion at a multidisciplinary cancer conference (MCC) for all cases of radiation for pleomorphic adenoma.  

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ARRO
Adjuvant RT Schedules for PA

• Microscopic residual disease or other high-risk features:
  – 50Gy in 20 - 25 daily fractions to the tumor bed *
    • Consider elective treatment to the remaining parotid
    • Consider elective treatment to the parapharyngeal space and infratemporal fossa for deep lobe involvement or post-total parotidectomy

• Gross residual disease:
  – 60Gy in 30 daily fractions*

• Usually no elective neck (nodal) irradiation for PA

• Consider including the scar and areas of potential dermal spread, especially for tumor spillage

• Setup: Supine, thermoplast mask, neck and knee rest, +/- bolus to the scar and potential areas of dermal spread

*Based on the PMH Guidelines although literature has also described doses up to ~70Gy$^{20,24}$
Potential Toxicities

Dermatitis, xerostomia, mucositis, dysgeusia, odynophagia/dysphagia that may require a G-tube, alopecia, **osteonecrosis, otitis, hearing loss, cholesteatoma, trismus, fibrosis**
7 years later...

Back to the case

- Referred back to ENT for left-sided **hearing loss & a bad smell**
  - Audiometry shows left **sensorineural hearing loss (SNHL)** - hearing aid
  - Examination shows significant wax that is removed to **show skin loss & exposed bone** – debrided every few months including removal of a cyst
  - Settles with Garamycin drops
Hearing loss after radiation

- Radiation to the inner ear has been shown to cause sensorineural hearing loss (SNHL) with damage to the stria vascularis, spiral ligament, basilar membrane or cells within the Organ of Corti.

- SNHL is described in 30-60% of patients after postoperative 3D Conformal Radiation Treatment (3DCRT) for parotid cancers treated to 60-65Gy in 30 daily fractions.

- Ipsilateral cochlea is usually close to the PTV and receives a dose >50Gy with 3DCRT.

- IMRT is able reduce the dose to the cochlea to <40-45Gy.

- Can IMRT prevent SNHL with cochlear-sparing (CS-IMRT)?
CS-IMRT lowered dose to the cochlea

COSTAR
Phase III RCT
110 pts w/parotid cancer
(pT1-4, N0-3, M0)

<table>
<thead>
<tr>
<th>Radiotherapy dose (Gy)</th>
<th>3DCRT (N = 54)</th>
<th>CS-IMRT (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median dose to the primary tumour and involved nodes</td>
<td>65.0 (64.9–65.0; 51)</td>
<td>65.0 (65.0–65.0; 54)</td>
</tr>
<tr>
<td>Mean dose to contralateral cochlea</td>
<td>6.1 (2.9–8.8; 51)</td>
<td>8.3 (6.6–9.3; 54)</td>
</tr>
<tr>
<td>Mean dose to ipsilateral cochlea</td>
<td>56.2 (44.6–61.0; 51)</td>
<td>35.7 (30.0–39.0; 54)</td>
</tr>
</tbody>
</table>
But provided no clinically significant differences in hearing.
COSTAR did help quantify toxicities

Grade 2+ at up to 60 months

- Fatigue
- Trismus
- Dryness
- Otalgia
- Tinnitus
- Otitis
- Hearing

3DCRT
CS-IMRT

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But not osteoradionecrosis...yet

• Osteoradionecrosis (ORN) may be defined as exposed irradiated bone that fails to heal in 3 months without evidence of tumour

• May be caused by radiation arteritis leading to a hypocellular, hypovascular & hypoxic environment

• The temporal bone is at particular risk due to its superficial position (like the mandible) and the external ear canal is more susceptible due to thin overlying skin and poor vasculature

• Osteoradionecrosis of the temporal bone is seen in 10-15% of patients receiving postoperative RT for parotid tumors with a mean time from treatment of 7-11 years\textsuperscript{26}
Simple Classification for Temporal Bone ORN

Localized

Presents with exposed dead bone in the external auditory canal (EAC), otalgia, & otorrhea

Diffuse

Presents with extensive involvement of the temporal bone, extreme boring pain, +++otorrhea, foul odor, and complications such as mastoid necrosis, fistula, exposed dura, meningitis, brain abscess, & facial nerve palsy

Classification described by Ramsden et al. Others include those by Marx, Epstein, Schwartz, & Notani based on a combination of physical & imaging findings.
Managing Temporal Bone ORN

From Kammeijer et al.  

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**ORN**

CT-scan: mastoid air cell destruction

- **No**
  - Localized ORN
    - Start/continue conservative treatment:
      - Regular careful cleaning
      - Eardrops (antibiotic/acid)
      - Prevent/avoid trauma
      - Sequestrectomy
      - 3-4 months follow-up
    - Localized

- **Yes**
  - Diffuse ORN
    - Diffuse A: Little pain and infection and intact functional hearing
      - Start/continue conservative treatment:
        - Regular careful cleaning
        - Eardrops (antibiotic/acid)
        - Prevent/avoid trauma
        - Sequestrectomy
        - 3-4 months follow-up
      - Diffuse A

    - Diffuse B: Severe pain and infection and/or no functional hearing
      - Subtotal petrosectomy
HBOT for ORN?

• Hyperbaric Oxygen Therapy (HBOT): Limited evidence for benefit in ORN

  – 1 RCT & 3 Cohorts
  • Highest level of evidence is from ORN96, a prospective, multi-centre, double-blind RCT terminated early due to worse outcomes in the HBOT arm (19% resolution of ORN with HBOT versus 32% with placebo)\textsuperscript{29}

  – Some guidelines such as Dana-Farber (2017) recommend against its use
Pentoxifylline: Weak evidence for benefit in 7 retrospective studies\textsuperscript{30}

Pentoxifylline has anti-TNF and vasodilatory effects while decreasing blood viscosity and clotting. Dosing is 200-400mg po tid. It is often given together with Tocopherol (Vitamin E) 1000IU po daily, an antioxidant.
2 years later...

Back to the case

• New left-sided facial spasms
• MRI shows 2 x 2cm mass high in the residual parotid at the skull base surrounding the styloid process
  – Low intensity on T1
  – High intensity on T2
  – Homogeneous enhancement post-Gad
• ENT performs a revision parotidectomy/debulking
  – A rind was left on the superior carotid and facial nerve to preserve function
  – Final pathology still suggests recurrent PA
6 months later...

• The mass grew back
• MRI shows a 4cm mass in the parotid bed encasing the carotid artery and invading the left temporal bone
  – T1 & T2 heterogenous
  – Also two new satellite nodules
• Another debulking suggests increased cellularity and that carcinoma could not be ruled out
Case continued

• Based on MRI findings, pathology, & rapid growth she is diagnosed with **Carcinoma Ex Pleomorphic Adenoma (CaXPA)**

• Staging shows no brain, nodal, lung, or bone metastases (**Stage IVB cT4b cN0 M0**)

• MCC suggests no room for further surgery and no role for chemotherapy, but **to consider re-irradiation**
Re-irradiation Treatment Plan

- Diagnostic MRI fused with planning CT
- Gross Disease to 66Gy in 1.1Gy/# BID
  - GTV: Gross mass & the 2 satellite nodules
  - CTV66: GTV + 5mm expansion cropped to anatomical structures not at risk + postoperative bed
  - PTV66: CTV + 3mm expansion
  - After comparison with the previous plan and estimation of cumulative doses, optPTV is cropped to the brain & brainstem PRV (critical OARs)
  - An intermediate dose (optPTV60) is determined to have safe overlap with brain, but still needs to be cropped to the brainstem for safety
- Elective nodes to 54Gy in 0.9Gy/# BID
  - CTV54: Left levels II-IV
  - PTV54: CTV + 3mm expansion
- Setup: 1.5cm bolus to cover gross disease, supine, arms at side, with thermoplast head & shoulder mask
DVHs for the Targets

![Graph showing DVHs for different structures and plans with data on dose, volume, and coverage.]

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>optPTV66</td>
<td>Approved</td>
<td>PARL</td>
<td>C1</td>
<td>121.8</td>
<td>100.0</td>
<td>100.1</td>
<td>5580.9</td>
<td>7102.9</td>
<td>6813.5</td>
</tr>
<tr>
<td></td>
<td>optLPTV54b</td>
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<td>PARL</td>
<td>C1</td>
<td>55.4</td>
<td>100.0</td>
<td>100.0</td>
<td>4958.4</td>
<td>6234.6</td>
<td>5690.2</td>
</tr>
<tr>
<td></td>
<td>optLPTV54a</td>
<td>Approved</td>
<td>PARL</td>
<td>C1</td>
<td>20.5</td>
<td>100.0</td>
<td>100.2</td>
<td>4953.5</td>
<td>6824.9</td>
<td>5823.4</td>
</tr>
<tr>
<td></td>
<td>PTV60</td>
<td>Approved</td>
<td>PARL</td>
<td>C1</td>
<td>37.7</td>
<td>100.0</td>
<td>100.0</td>
<td>5549.1</td>
<td>6929.4</td>
<td>6314.9</td>
</tr>
<tr>
<td></td>
<td>LCTV54</td>
<td>Approved</td>
<td>PARL</td>
<td>C1</td>
<td>35.7</td>
<td>100.0</td>
<td>100.1</td>
<td>5226.4</td>
<td>7044.1</td>
<td>6107.8</td>
</tr>
<tr>
<td></td>
<td>GTV</td>
<td>Approved</td>
<td>PARL</td>
<td>C1</td>
<td>45.5</td>
<td>100.0</td>
<td>100.0</td>
<td>5042.3</td>
<td>7021.6</td>
<td>6738.0</td>
</tr>
<tr>
<td></td>
<td>CTV66</td>
<td>Approved</td>
<td>PARL</td>
<td>C1</td>
<td>100.3</td>
<td>100.0</td>
<td>100.1</td>
<td>4867.9</td>
<td>7089.1</td>
<td>6645.7</td>
</tr>
</tbody>
</table>
DVHs for the Organs at Risk (OARs)
<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose Constraint</th>
<th>Risk</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Dmax &lt; 60Gy</td>
<td>Symptomatic Necrosis</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Brain</td>
<td>Dmax &lt; 72Gy</td>
<td>Symptomatic Necrosis</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Dmax &lt; 54Gy</td>
<td>Neuropathy/Necrosis</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Rt Parotid</td>
<td>Mean Dose &lt;= 26Gy</td>
<td>Salivary flow</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Lens</td>
<td>Mean Dose &lt;= 7Gy</td>
<td>Cataracts at 5 years</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>Rt Submandibular</td>
<td>Mean Dose &lt;= 39Gy</td>
<td>Xerostomia</td>
<td>N/A</td>
</tr>
<tr>
<td>Chiasm</td>
<td>Dmax &lt; 50Gy</td>
<td>Optic Neuropathy</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Spinal Canal</td>
<td>Dmax &lt; 48Gy</td>
<td>Myelopathy</td>
<td>&lt;0.2%</td>
</tr>
<tr>
<td>Mandible</td>
<td>V70Gy &lt;= 0.1cc</td>
<td>Osteonecrosis</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Lt Cochlea</td>
<td>Dmax &lt; 40Gy</td>
<td>Sensorineural Hearing Loss</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Rt Cochlea</td>
<td>Dmax &lt; 40Gy</td>
<td>Sensorineural Hearing Loss</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Larynx</td>
<td>Mean Dose &lt;= 45 Gy</td>
<td>Edema</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Larynx</td>
<td>V50Gy &lt;= 67%</td>
<td>Aspiration</td>
<td>&lt;30%</td>
</tr>
</tbody>
</table>

*All constraints are in 2Gy per fraction and adapted from RTOG 1008*

Consent included these risks, with possible higher rates of complications where tolerances were not met and due to the previous treatment.
Peer Review and Audit

- The ipsilateral cochlea could not be preserved without compromising coverage to the GTV. Given significant baseline hearing loss, the GTV was not compromised here.

- Coverage for the CTV66, CTV60, and GTV was compromised adjacent to the brainstem to maintain cumulative dose tolerances to this critical OAR. After significant discussion, it was felt that the risks of treating this area including cumulative dose from previous treatment, even with hyperfractionation, outweighed the benefits and the plan was approved.
2 years later...

• She has persistent left-sided hearing loss, mild dysphagia, and mild facial weakness, but is otherwise well
Compressed VII at the base of skull?

- Cribiform Plate (I)
- Optic Canal (II)
- Superior Orbital Fissure (IV, V1, VI)
- Foramen Rotundum (V2)
- Foramen Ovale (V3)
- Stylomastoid Foramen (VII) – Facial Nerve
- Intermediate Jugular Foramen (IX, X, XI)
- Hypoglossal Canal (XII)
Carcinoma Ex-Pleomorphic Adenoma (CaXPA)

- See CaXPA ARROCase by A Albert et al for more details

In brief:
- 4% of SGTs and 12% of salivary gland cancers (SGCs)
- Develops in association with a pleomorphic adenoma with increasing risk of CaXPA with increasing time of in-situ PA
- But 80% of patients do not have a prior history of PA
- Other risk factors include age, previous ionizing radiation, and larger or recurrent benign disease
- Median age is 55
- Presents as a sudden increase in growth, pain, facial paralysis, tingling, or trismus (22% local recurrence of another salivary tumor, 56% have nodal metastases, and 44% have distant mets to lung, bone, GI, CNS, or kidneys)
- Mixed findings on MRI (usually heterogeneous on T1, low on T2,
  - Apparent Diffusion Coefficient is usually low (compared to high for PAs)
  - Poor survival (25-65% at 5-10 years and 0-38% at 20 years)
CaXPA is a minority

Salivary Gland Cancers (SGCs) represent ~6% of all H&N cancers

SGCs are found in 15-35% of parotid tumors

CaXPA represents only 1-6% of all parotid tumors\(^6\)

Mucoepidermoid cancer is 1-12%

Acinic Cell Carcinoma is 1-9%

Others
Workup & Staging

- Similar **workup as for a neck mass**
- MRI better for perineural spread & intracranial or parapharyngeal extension
- CT Chest
- Dental, nutrition, & SLP assessment
- Other investigations or multidisciplinary cancer conference as clinically indicated

<table>
<thead>
<tr>
<th>cT or pT</th>
<th>N Stage (pN or cN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 &lt;2cm</td>
<td>N0: N1 N2a N2b N2c</td>
</tr>
<tr>
<td>T2 2.1-4cm</td>
<td>N2: N1 N2a N2b N2c</td>
</tr>
<tr>
<td>&gt;4cm +/-</td>
<td>N3: N1 N2a N2b N2c</td>
</tr>
<tr>
<td>T3 EPE(+)</td>
<td>N2: N1 N2a N2b N2c</td>
</tr>
<tr>
<td>T4a Invasion¹</td>
<td>N3: N1 N2a N2b N2c</td>
</tr>
<tr>
<td>T4b Invasion²</td>
<td>N3: N1 N2a N2b N2c</td>
</tr>
<tr>
<td>M1 Distant Mets</td>
<td>N3: N1 N2a N2b N2c</td>
</tr>
</tbody>
</table>
# Treatment for Salivary Gland Cancers

## Local Disease

The extent of primary surgical treatment depends on location (parotid, submandibular gland, or other gland), T/N-status, and grade. **Adjuvant RT is based on high-risk features for local recurrence.** **Definitive RT is second-line for unresectable disease.**

### N0 Neck

- Lack of consensus.
- Consider observation for benign or low-grade malignancies.
- Elective neck dissection (II-V, +/- I) for high-grade*, T3+, submandibular involvement, EPE(+), or LVI. **Elective neck RT for high-risk features of nodal spread.**

### N+ Neck

- Selective neck dissection (II-V, +/- I or based on involved nodal location) and adjuvant RT.

## Recurrent Disease

- Surgery is first line and adjuvant RT if feasible.
- If unresectable, consider RT +/- systemic treatment.
- If unresectable and RT not feasible, consider systemic treatment.

## Metastatic Disease

- Usually palliative RT or systemic treatment.
- Metastectomy may be considered for select patients depending on site (e.g. limited lung mets), when the primary is controlled, complete resection of mets is possible, and patient can tolerate surgery.

## Follow-up

- **Similar schedule as for pleomorphic adenoma**
- Long-term follow-up is strongly recommended, especially for certain tumor types like Adenoid Cystic Carcinoma that have a protracted course
- Includes chest imaging

---

*retrospective studies suggest high-risk pathology is more important than stage for nodal spread and usually warrants a neck dissection.*

**some guidelines suggest elective neck RT for high-risk features in undissected neck regions**

---

*ARRO*
## Adjuvant RT indications for SGCs

### High-Risk Features

#### Local Recurrence

<table>
<thead>
<tr>
<th>High-risk pathologies:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td></td>
</tr>
<tr>
<td>High-grade mucoepidermoid ca</td>
<td></td>
</tr>
<tr>
<td>Adenoid cystic ca</td>
<td></td>
</tr>
<tr>
<td>CaXPA</td>
<td></td>
</tr>
<tr>
<td>Other high-grade tumours</td>
<td></td>
</tr>
<tr>
<td>Positive margins</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion or spread (microscopic or major nerve)</td>
<td></td>
</tr>
<tr>
<td>Deep parotid lobe cancer</td>
<td></td>
</tr>
</tbody>
</table>

| T3+ |       |
| Close margins (<1-5mm) |       |
| Bone involvement        |       |
| Submandibular gland primary |   |

#### Nodal Recurrence

| High-risk pathologies |       |
| Locally Advanced (T3+ or N+) |     |
| Extracapsular extensions (ECE) |   |

| LVI | Relative |
| Facial nerve paralysis |        |

### Relative

| RTOG 1008 allows omitting elective nodal radiation for early Adenoid Cystic Carcinomas (pT1-2 N0) |

### Sources


---

**ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY**

**ARRO**
Radiation Schedules for SGCs

Still no mature data from RCTs so guidelines are based on several retrospective studies that have consistently demonstrated benefit of adjuvant RT in select patients with high-risk features

<table>
<thead>
<tr>
<th>Unresectable</th>
<th>Definitive RT may provide local control (~40% vs. 81% for surgery + RT at 10 years) &amp; symptom palliation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast Neutron Therapy is rarely used due to lack of availability</td>
</tr>
<tr>
<td></td>
<td>May consider proton or carbon ions on clinical trials</td>
</tr>
<tr>
<td></td>
<td>Target volumes are similar as in the adjuvant setting</td>
</tr>
<tr>
<td></td>
<td>70 Gy in 35 daily# to gross disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjuvant*</th>
<th>For <strong>high-risk features, adjuvant RT</strong> may provide absolute benefit up to ~30-40% in LC &amp; 40% in OS at 5-years¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boost to 66Gy in 33 daily# for close (≤ 1-5mm)/+margin or +pathologic extracapsular nodal extension (+ECE)</td>
</tr>
<tr>
<td></td>
<td>60Gy in 30# for regions at high risk for microscopic disease (tumor bed or involved nodal regions)</td>
</tr>
<tr>
<td></td>
<td>54-56Gy in 30-33# for elective nodal regions (indications include high-risk path or advanced ca (T3+, N+))</td>
</tr>
<tr>
<td></td>
<td>For involvement of a major nerve, consider coverage (54-56Gy) along course to skull base</td>
</tr>
<tr>
<td></td>
<td>IMRT/VMAT is usually used to spare OARs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reirradiation (Re-RT)**</th>
<th>Clinical trial if available (including proton or carbon ion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If no clinical trial consider re-RT* +/- systemic treatment</td>
</tr>
</tbody>
</table>

Sources: Mendenhall 2005, PMH Guidelines 2019, UICC 2015, RTOG 1008 2012²¹, ³¹, ³²
*For detailed treatment volumes see Appendix 4
**For reirradiation treatment strategies see Appendix 5
Not so fast...photons are still used more than neutrons

• RTOG-MRC phase III compared fast neutrons to photons for unresectable SGTs\textsuperscript{35}
  – Neutrons significantly improved local control (56% vs. 17% at 10-years) and less distant metastases, but no difference in OS
  – Severe late effects and limited centres around the world are why this technique is rarely used

• Protons and carbon ions are experimental and may reduce late toxicities\textsuperscript{37}
What about Chemoradiation?

• RTOG 1008 is an ongoing randomized phase II comparing adjuvant chemoradiation (CRT) vs. RT alone for SGCs treated with surgery. Doses of 60-66Gy in standard (2Gy) fractionation +/- concurrent Cisplatin.32
  – Study complete date is October 2028

• GORTEC SANTAL is an ongoing phase III including SGCs and nasal tumors also comparing adjuvant CRT vs. RT alone. **Doses of 66-70Gy** in standard fractionation +/- concurrent Cisplatin.

• Retrospective studies comparing adjuvant CRT to RT in resected SGCs with high-risk features using multivariate and propensity-matched analyses showed mixed results:
  – One that only including adenoid cystic carcinoma suggested improved local control with CRT (97% vs. 67% at 8-years), even better on subgroup analysis with Stage III-IV disease, margin+, or PNI
  – Two suggested no difference in OS or PFS
  – Two suggested inferior OS
Re-Irradiation (Re-RT) for SGCs

• Many locoregionally recurrent H&N cancers after radiation cannot be salvaged by surgery
• Response rates for chemotherapy in this setting is limited (median survival 7.4 months)\textsuperscript{14}
• Re-irradiation is potentially curative for some patients with unresectable disease, but...
  – theoretical risk of development of radiation resistance (in a cancer that is generally radioresistant) and dose is important
  – increased risk of severe complications
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Re-RT Toxicities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td>Mucositis</td>
<td>Grade 3-4 in 14%–26% of patients</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td>Dysphagia</td>
<td>Significant recovery after at least 6 months since the initial treatment, with continued recovery to 2-3 years</td>
</tr>
<tr>
<td></td>
<td>Spinal cord myelopathy</td>
<td>May be &lt;1% for cumulative dose &lt; 60Gy accounting for recovery (e.g. 50% at one year)</td>
</tr>
<tr>
<td></td>
<td>Carotid artery rupture</td>
<td>3% at a median of 7.7mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76% are fatal</td>
</tr>
<tr>
<td></td>
<td>Osteoradionecrosis</td>
<td>In &lt; 7%</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td>In 5-20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>From infection due to leucopenia, aspiration, and fatal hemorrhage from carotid rupture</td>
</tr>
</tbody>
</table>

Source: Kim et al, 2017[^36]
# Prognostic Factors for Re-RT

<table>
<thead>
<tr>
<th>For better local control &amp; overall survival</th>
<th>For less toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage surgery or debulking prior to Re-RT</td>
<td>Lower cumulative dose to OARs</td>
</tr>
<tr>
<td>Site (Naso, larynx, &amp; neck &gt; others)</td>
<td>No concurrent chemotherapy</td>
</tr>
<tr>
<td>Histology/Low Grade</td>
<td>Older age</td>
</tr>
<tr>
<td>More time since prior RT</td>
<td>Mucosal involvement/ulceration</td>
</tr>
<tr>
<td>Higher delivered dose</td>
<td>Larger volumes</td>
</tr>
<tr>
<td>T Stage/Size</td>
<td>Re-RT schedules (1.1Gy BID &gt; 1.5Gy BID)</td>
</tr>
<tr>
<td>Concurrent chemotherapy</td>
<td>Modality (PBT &gt; 3DCRT)</td>
</tr>
<tr>
<td>No previous chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Younger Age</td>
<td></td>
</tr>
</tbody>
</table>

Source: Kim et al, 2017³⁶
Future Directions

• Answer the chemotherapy question:
  – RTOG 1008 results pending
  – GORTEC SANTAL is recruiting

• Bring targeted therapies to mainstream practice\textsuperscript{38}
  – Phase I/II trials ongoing
  – For advanced/recurrent/metastatic SGCs NCCN suggests treatment for targetable mutations based on limited evidence such as:
    • Complete androgen blockade for androgen receptor+
    • Larotrectinib for NTRK gene fusion+
    • Trastuzumab for HER2+

• Improve understanding of predictive features for recurrence to improve patient selection for radiation

• Develop improved radiation strategies for unresectable disease or re-irradiation
Salivary Gland Tumor Summary

- Salivary Gland Tumors are rare, and as a result so is the evidence for their management
- Surgery is first-line for benign and malignant disease
- Adjuvant radiation is indicated for features suggesting high-risk for local or nodal recurrence
- Definitive radiation treatment is indicated for unresectable disease
- Re-irradiation is possible
APPENDIX

1: References
2: Photo References
3: Epidemiology of Salivary Gland Tumors by Site
4: Adjuvant RT Volumes for RTOG 1008
5: Reirradiation Treatment Strategies
Appendix 1: References

5. @RadOncMnemonics. Feb 2018.
Appendix 1: References


Appendix 1: References


Appendix 2: Photo References

### Appendix 3: Epidemiology of Salivary Gland Tumors by Site

**TABLE 56-1 Sites of Occurrence of Primary Epithelial Salivary Gland Tumors**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Cases</th>
<th>Parotid</th>
<th>Submandibular</th>
<th>Sublingual</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al.³</td>
<td>13,749</td>
<td>64%</td>
<td>10%</td>
<td>0.3%</td>
<td>23%</td>
</tr>
<tr>
<td>Spiro⁴</td>
<td>2,807</td>
<td>70%</td>
<td>8%</td>
<td>Included with minor</td>
<td>22%</td>
</tr>
<tr>
<td>Seifert et al.³</td>
<td>2,579</td>
<td>80%</td>
<td>10%</td>
<td>1.0%</td>
<td>9%</td>
</tr>
<tr>
<td>Evenson and Cawson²</td>
<td>2,410</td>
<td>73%</td>
<td>11%</td>
<td>0.3%</td>
<td>14%</td>
</tr>
</tbody>
</table>

**TABLE 56-2 Frequency of Malignant Salivary Tumors at Different Sites**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Cases</th>
<th>Parotid</th>
<th>Submandibular</th>
<th>Sublingual</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al.³</td>
<td>13,749</td>
<td>32%</td>
<td>41%</td>
<td>70%</td>
<td>49%</td>
</tr>
<tr>
<td>Spiro⁴</td>
<td>2,807</td>
<td>25%</td>
<td>43%</td>
<td>Included with minor</td>
<td>82%</td>
</tr>
<tr>
<td>Seifert et al.³</td>
<td>2,579</td>
<td>20%</td>
<td>45%</td>
<td>90%</td>
<td>45%</td>
</tr>
<tr>
<td>Evenson and Cawson²</td>
<td>2,410</td>
<td>15%</td>
<td>37%</td>
<td>86%</td>
<td>46%</td>
</tr>
</tbody>
</table>

**TABLE 56-3 Parotid Tumors**

<table>
<thead>
<tr>
<th></th>
<th>Ellis et al.³</th>
<th>Evenson and Cawson²</th>
<th>Thackray and Lucas⁵</th>
<th>Enroth⁶</th>
<th>Foote and Frazell⁷</th>
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</thead>
<tbody>
<tr>
<td>Benign Tumors</td>
<td>8,222</td>
<td>1,756</td>
<td>651</td>
<td>2,158</td>
<td>764</td>
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<tr>
<td>Pleomorphic adenoma</td>
<td>53.0%</td>
<td>63.3%</td>
<td>72.0%</td>
<td>76.8%</td>
<td>58.5%</td>
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<tr>
<td>Warthin tumor</td>
<td>7.7%</td>
<td>14.0%</td>
<td>9.0%</td>
<td>4.7%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>1.9%</td>
<td>0.9%</td>
<td>0.6%</td>
<td>1.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Basal cell adenoma</td>
<td>1.4%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>3.7%</td>
<td>7.1%</td>
<td>1.8%</td>
<td>—</td>
<td>0.7%</td>
</tr>
<tr>
<td>Total</td>
<td>67.7%</td>
<td>85.3%</td>
<td>83.4%</td>
<td>82.5%</td>
<td>65.8%</td>
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</table>

<table>
<thead>
<tr>
<th>Malignant Tumors</th>
<th>Ellis et al.³</th>
<th>Evenson and Cawson²</th>
<th>Thackray and Lucas⁵</th>
<th>Enroth⁶</th>
<th>Foote and Frazell⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>9.6%</td>
<td>1.5%</td>
<td>2.3%</td>
<td>4.1%</td>
<td>11.8%</td>
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<tr>
<td>Acinic cell carcinoma</td>
<td>8.6%</td>
<td>2.5%</td>
<td>1.2%</td>
<td>3.1%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>2.0%</td>
<td>2.0%</td>
<td>3.3%</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Malignant mixed tumor</td>
<td>2.5%</td>
<td>3.2%</td>
<td>4.1%</td>
<td>1.5%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2.1%</td>
<td>1.1%</td>
<td>1.0%</td>
<td>0.3%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Other</td>
<td>7.5%</td>
<td>4.4%</td>
<td>4.7%</td>
<td>6.3%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Total</td>
<td>32.3%</td>
<td>14.7%</td>
<td>16.6%</td>
<td>17.5%</td>
<td>34.2%</td>
</tr>
</tbody>
</table>

Source: Neville et al, 2009⁶
### Appendix 4: Adjuvant RT Volumes - RTOG 1008

#### All SGCs

**PTVx**: 2.5-5mm margin on the corresponding CTVx

**PTV3**: Boost to 66Gy in 33# for close (≤ 1mm) or +margin, or +pathologic extracapsular nodal extension (+ECE)*

**PTV2**: 60Gy in 30# over 6wks for regions at high risk for microscopic disease**

**PTV1**: 54Gy in 30# for elective nodal regions considered at risk or coverage to the base of skull for gross involvement of a major nerve

#### Parotid Gland

**CTV1: Primary**

Preop volume of the involved parotid gland (GTV) and postop surgical bed***

Infratemporal fossa to the stylomastoid foramen

Surgical scar

+/- Deep lobe (post-superficial parotidectomy)

+/- Parapharyngeal space (for deep lobe tumors or post-total parotidectomy)

+/- Facial nerve canal through the petrous bone to the foramen ovale (if gross CN VII PNI or for Adenoid Cystic Carcinoma)

**CTV1: Elective nodal regions**

Usually ipsilateral Ib-IV****

+/- Ipsilateral Ib and retrostyloid (if level II involvement)

+/- Ipsilateral V (if level II, III, or IV involvement)

---

#### Submandibular & Sublingual Gland

**CTV1: Primary**

Preop volume (GTV) & postop surgical bed*** including entire submandibular space

Surgical scar

+/- Up to the hypoglossal canal (if gross XII involvement)

+/- Up to the foramen ovale (if gross lingual or inferior alveolar n. involved)

+/- Proximal mandible to the mandibular foramen (if gross inferior alveolar n. involved)

**CTV1: Elective nodal regions**

Usually ipsilateral Ib-IV****

+/- Contralateral I & II (if ipsilateral level I involved)

+/- Retrostyloid (if level II involvement)

+/- Ipsilateral V (if level II, III, or IV involvement)

---

#### Minor Salivary Gland

**CTV1: Primary**

Preop volume (GTV) and postop surgical bed***

+/- Along any named nerve to the skull base (if gross involvement)

Surgical scar

Preop volume (GTV) and postop surgical bed***

**CTV1: Elective nodal regions**

Usually ipsilateral Ib-IV****

+/- Contralateral neck (for primaries <1cm from the midline)

+/- Retrostyloid (if level II involvement)

+/- Ipsilateral V (if level II, III, or IV involvement)

---

*CTV3 includes the postop surgical bed +5mm margin & entire nodal level of any pathological ECE+ nodes

**CTV2 includes the postop surgical bed & site of involved named nerves +1cm margin & the entire nodal level of any N+

***Usually GTV + 1.5 - 2cm margin respecting anatomic boundaries not at risk for microscopic disease

****Elective nodal irradiation may be omitted for the N0 neck in early Adenoid Cystic Carcinoma (pT1-2)
## Appendix 5: Re-RT Treatment Strategies

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
</table>
| Unresectable | Re-RT indications are similar to other definitive RT SGC cases with consideration for time from last treatment (>6 month disease-free interval)  
Re-RT can provide local control, symptom palliation, and may be potentially curative  
>60-66Gy may be tumoricidal and dose thought to be important (~40% recur in high-dose region)  
No consensus for technique, volumes, or schedule – consider a clinical trial  
Hyperfractionation of 1.2-1.2Gy BID may be effective in sparing late-responding normal tissues  
Hypofractionation or ablative doses (~30Gy/5#) may overcome radioresistance  
PBT and Carbon ion are investigational  
PBT may decrease acute and late toxicities due to minimal entrance and exit$^{37}$  
Carbon ion may be more biologically effective without increasing toxicity  
Volumes are based on a balance of risk and benefit and should consider cumulative doses  
IMRT CTVp: ~0.5-2cm from the GTV  
CTVn: no consensus due to unexpected lymph drainage in previously treated necks. May consider similar guidelines as for untreated necks |
| Adjuvant | Adjuvant re-RT indications are similar to other adjuvant RT SGC cases with consideration for time from treatment  
No consensus for technique, volumes, or schedule; consider as above |
| Chemotherapy | No consensus – consider a clinical trial  
Phase III (RTOG 1008) results are pending, GORTEC-SANTAL is recruiting, and retrospective results are mixed  
Phase II trials for targeted therapies are ongoing  
EORTC-1206-HNCG RCT for CT vs. ADT in AR+ SGCs |

Sources: Kim 2017, Romesser 2016$^{36,37}$