Adenoid Cystic Carcinoma (ACC) of the Head and Neck

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Outline

• Case
  – Clinical Presentation
  – Workup/Diagnosis
  – Management
    • Surgery
    • Adjuvant radiation
      – CT simulation
      – Target delineation
      – Plan evaluation
  – Follow-up

• Background
• Workup
• Management
  – Surgery
  – Radiation
    • Postop vs definitive
    • Target selection
      – Cranial nerve coverage
      – Elective nodal RT
    • Modalities
  – Chemotherapy
• Future Directions
Case: Clinical Presentation

- **HPI:** 65-year-old man referred to ENT for painful, enlarging oral cavity mass along upper gum (over 3-4 months)
- **ROS:** No bleeding, neck masses, weight loss, formication, numbness, tingling, or weakness
- **SH:** No history of tobacco or alcohol use
- **PMH, PSH, meds/allergies, FH** otherwise non-contributory
- **Physical exam:** 3.5cm submucosal mass, along gingivobuccal sulcus of left maxillary alveolar ridge, crosses midline
  - No palpable facial, submental, submandibular, cervical, or supraclavicular adenopathy
  - Cranial nerves II – XII intact
  - Maxillary dentition absent; mandibular teeth present and without decay
  - No other oral lesions, ulcers, or evidence of bleeding
Case: Diagnostic Workup

• ENT performed **flexible nasopharyngolaryngoscopy**
  – Submucosal mass extends into left nasal cavity to inferior turbinate.
  – Remainder of visualized right nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx without abnormalities

• **Biopsy** of gingival mass: *+Adenoid cystic carcinoma*
  – Predominantly cribriform pattern (Grade 2)

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<tr>
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<tbody>
<tr>
<td>1</td>
<td>Typical cribriform pattern exclusively</td>
<td>Tubular and cribriform areas without solid components</td>
</tr>
<tr>
<td>2</td>
<td>Cribriform pattern about equally mixed with solid areas (showing basaloid or anaplastic features)</td>
<td>Pure cribriform pattern or mixed with &lt;30% solid areas</td>
</tr>
<tr>
<td>3</td>
<td>Basaloid or anaplastic features predominantly</td>
<td>Predominantly solid pattern (&gt;30%)</td>
</tr>
</tbody>
</table>
Case: Diagnostic Workup

- **CT max/face with IV contrast:**
  - Infiltrative mass centered in region of left premaxilla, 3.8cm
  - Involves left nasolabial fold and protrudes into inferior nasal cavity
  - Gross bone invasion of premaxilla, ~1cm extension beyond midline
  - Extends slightly into maxillary sinus
  - No orbital involvement
  - No facial, cervical, or parotid adenopathy

- **CT Chest:** no distant mets
Case: Diagnostic Workup

- MR face, oral cavity, orbit without/with IV contrast:
  - Mass extends superiorly into superficial musculoaponeurotic system of face
  - No definite evidence of PNI
    - No extension along infraorbital or mental nerve
  - Cavernous sinus appears normal
Case: Initial Management (Surgery)

- Head and Neck Multidisciplinary Tumor Conference recommended primary surgery and postop RT

- First, en bloc tumor resection was performed via lateral rhinotomy incision
  - Left maxillectomy, total ethmoidectomy, skull base dissection, midface reconstruction, orbital preservation
  - Right fibular osteocutaneous free flap; dental implants placed (x4)
  - Left suprahyoid neck dissection

August 20, 2021
Case: Surgical Pathology

- Adenoid cystic carcinoma, 4.5 x 2.3 x 2.2 cm
  - Cribriform pattern, 20% solid component
  - Unifocal tumor involving premaxilla, anterior maxilla, palate, maxillary sinus, nasal cavity
  - Microscopic perineural invasion present, focal, involving small-caliber nerves (<0.1mm)
    - No malignancy identified in the portion of V2 excised with resection margins
  - No LVSI
  - Multiple specimen margins involved by invasive tumor
    - All separately submitted margins uninvolved
- 0/2 lymph nodes involved (left level 1B)

https://www.nature.com/articles/modpathol200995.pdf
Case: Postoperative Course

• Appx 2-3 weeks postop, he developed L nasolabial dehiscence: 2x2cm area of nonviable, infected tissue
  – Initially managed with p.o. antibiotics

• He was taken back to OR (5 weeks after primary surgery) for debridement and surgical revision of partial free flap loss
  – Skin paddle of Fibula Free Flap was non-viable
  – Underlying fascia and bone were viable
  – He developed minor oral-nasal fistula

• Adjuvant radiation start delayed until ~ 8 weeks postop
Case: Adjuvant Radiation

- CT simulation:
  - **Position:** Supine, arms at side, shoulders down, head extended
  - **Immobilization:** thermoplastic Aquaplast head mask, AccuFix board with shoulder depression mechanism and hand bars
  - **Bolus:** 5mm along surgical scar of left face
  - **Additional instructions:**
    - IV contrast
    - Oral stent (to move lower jaw inferiorly, away from treatment field)
    - Fuse CT images with postop MRI Head, T1+C
Case: Adjuvant Radiation

RT Volumes:
1. **CTV1** = CTV2 + CNV2 to foramen rotundum + CNV3 to foramen ovale + CN VII to stylomastoid foramen + skull base/low cavernous sinus. **No elective nodal irradiation.**
2. **CTV 2** = tumor bed + 5mm, edited for boundaries to tumor spread
3. **PTV1** = CTV1 + 3mm
4. **PTV2** = CTV2 + 3mm

**RT Prescription:**
- **PTV1**: 52.8 Gy at 1.6 Gy per fraction, QD
- **PTV2**: 66 Gy at 2 Gy per fraction, QD
- Total fractions: 33
- Total treatment days: 33

**Concurrent chemo**: No
**Technique**: IMRT SIB
**Beam Energy**: 6MV photons
**IGRT**: CBCT prior to each fx
**Bolus**: 5mm to facial incision
Case: Adjuvant Radiation

IMRT Isodose Plan (6MV photons)

Shaded Volumes:
- PTV1
- PTV2

Isodose lines (IDL):
- White IDL: 105% rx
- Red IDL: 100% rx
- Yellow IDL: 95% rx
- Cyan IDL: 90% rx
- Orange IDL: 80% rx
- Green IDL: 50% rx

Where “rx” refers to PTV2 prescription dose (66Gy). Therefore, 80% rx (orange IDL) = PTV1 prescription dose (0.8 x 66 Gy = 52.8 Gy)
### Case: Adjuvant Radiation

<table>
<thead>
<tr>
<th>Target Coverage Goals/ Heterogeneity Constraints</th>
<th>Major OAR Constraints</th>
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<tbody>
<tr>
<td>Structure</td>
<td>DVH Point</td>
</tr>
<tr>
<td>PTV</td>
<td>D95%</td>
</tr>
<tr>
<td>PTV</td>
<td>D99%</td>
</tr>
<tr>
<td>PTV</td>
<td>V110% Rx</td>
</tr>
<tr>
<td>PTV</td>
<td>D0.03cc</td>
</tr>
</tbody>
</table>

- **Met primary objective**
- **Met secondary objective**
- **Did not meet objective**

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Case: Follow-up

Treatment Course:

- By the end of RT, he developed grade 3 dysphagia, grade 3 oral mucositis, and grade 2 weight loss requiring opioids for pain, feeding tube placement, and hospitalization (10 days) for failure to thrive
  - Hospitalization/G-tube placement occurred just after RT completion

Post-RT Follow-up:

- Followed q3mo by ENT with head and neck exam and nasal endoscopy

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months post</td>
<td>OR for sinus endoscopy, bilateral nasal/left maxillary sinus debridement due to occlusive crusting and chronic sinusitis - Mandibular stretching for grade 3 trismus</td>
</tr>
<tr>
<td>9 months post</td>
<td>OR for debridement, mandibulotomy with plating, and reconstruction (left radial free flap) of grade 3 oral-nasal fistula with ORN</td>
</tr>
<tr>
<td>18 months post</td>
<td>Completed 30 treatments of HBO</td>
</tr>
<tr>
<td>22 months post</td>
<td>OR for removal of maxillary hardware with excisional wound debridement due to open wound and hardware exposure</td>
</tr>
</tbody>
</table>

Now 3 years since RT: NED (exam, CT maxface/neck and chest)

- Significant asymmetry, grade 3 fibrosis, and grade 1 hyperpigmentation of midface
- Still 100% G tube dependent (since end of RT)
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• Future Directions
Adenoid Cystic Carcinoma (ACC): The Basics

• Rare type of adenocarcinoma
  – 1,300 cases/yr in US, M:F 2:3, ↑50-60 y.o.
  – Most relevant studies are small, retrospective

• Most commonly arises in major and minor salivary glands of head and neck
  – Also can develop in lacrimal glands, ceruminous glands, larynx, trachea, paranasal sinuses, etc.

• Symptoms depend on tumor location
  – Often painless mass in head/neck
  – Neuro deficit indicates advanced disease

• Tendency for PNI and hematogenous spread to distant organs
Background: Clinical Course

• Locally aggressive
  – Grade determined by growth pattern
    • Grade I (predominantly tubular), Grade II (predominantly cribriform), Grade III (solid > 30 %)
  – T4: ~30-50%
  – +PNI: ~50-70%
  – Limited nodal spread (<10%)

• Indolent, but often aggressive course
  – High rates of survival (5y OS: ~80%, 15y OS: ~40%), but most pts progress
  – Followup should continue >15 years, if possible

• Most common site of DMs: lungs
  – Other sites of DMs: liver, brain, bone
  – DM is most common type of disease progression (>1/3)

https://radiopaedia.org/articles/perineural-spread-of-tumour

Yeung et al., 2009

Thariat et al., 2008
Diagnostic Workup

Complete head and neck exam (+ fiberoptic examination)
FNA or core needle biopsy
CT and MRI with contrast of skull base → clavicles
  → MRI is best radiographic study to evaluate PNI
CT Chest (with or without contrast)
Dental evaluation
Preanesthesia studies (preop assessment)
Nutrition and speech/swallowing evaluation
Multidisciplinary evaluation
Baseline eye, audiometry, and/or neuroendocrine function evaluation, when pertinent
How to Stage (AJCC 8th Edition)

• Primary tumor located in **major** salivary gland: refer to “Major Salivary Glands” chapter in “Head and Neck” section (or see next slide)

• Primary tumor located in **minor** salivary gland or other glandular organ: refer to relevant site chapter, often in “Head and Neck” section
  – Ex: ACC of hard palate → “Oral Cavity”

### AJCC 8th Edition Staging: Major Salivary Glands (Parotid, Submandibular, Sublingual)

<table>
<thead>
<tr>
<th>T Category</th>
<th>cN Category</th>
<th>pN Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1:</strong> ≤ 2cm, no EPE</td>
<td><strong>c/pN1:</strong> single ipsi node, ≤ 3cm, no ENE</td>
<td><strong>M1:</strong> any distant mets</td>
</tr>
<tr>
<td><strong>T2:</strong> &gt;2cm, ≤ 4cm, no EPE</td>
<td><strong>cN2a:</strong> single ipsi node, &gt;3cm, ≤ 6cm, no ENE</td>
<td></td>
</tr>
<tr>
<td><strong>T3:</strong> &gt;4cm and/or EPE(+)</td>
<td><strong>cN2b:</strong> multiple ipsi nodes, ≤6 cm, no ENE</td>
<td></td>
</tr>
<tr>
<td><strong>T4a:</strong> invades skin, mandible, ear canal, and/or facial nerve</td>
<td><strong>cN2c:</strong> b/l or c/l nodes, ≤6cm, no ENE</td>
<td></td>
</tr>
<tr>
<td><strong>T4b:</strong> invades skull base and/or pterygoid plates, and/or encases carotid artery</td>
<td><strong>cN3a:</strong> any node &gt;6cm, no ENE</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>cN3b:</strong> any node with clinically overt ENE(+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>pN3a:</strong> same</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>N3b:</strong> single ipsilateral node &gt;3cm with ENE(+) or multiple ipsi, c/l, or b/l nodes any with ENE (+)</td>
<td></td>
</tr>
</tbody>
</table>

### Key Terms
- **EPE:** extraparenchymal extension (clinical or macroscopic only)
- **Ipsi:** ipsilateral
- **ENE:** extranodal extension (any)
- **c/l:** contralateral
- **b/l:** bilateral
General Management Overview

Resectable (cT1-T4a)\textsuperscript{1} → Complete resection → PORT
• Always for ACC!

Unresectable (cT4b)\textsuperscript{1} → Definitive RT +/- chemo

\textsuperscript{1}Listed T stages only serve as a guide and do not represent all resectable or unresectable. Some very advanced cases may still be resectable and some less advanced ones may not be (or patient is not medically operable).

* Acceptable strategy per...

- Management of Salivary Gland Malignancy: ASCO Guideline
  Geiger, JCO 2021

- NCCN Guidelines Version 3.2021
  Salivary Gland Tumors
Surgical Management

- Radical resection to achieve negative margins is primary treatment
  - Definitive RT associated with worse locoregional control and survival
  - Close/involved margins associated with inferior LRC
- For cN+ neck, perform ipsi neck dissection of involved and at risk stations, up to levels I-V
- Facial nerve preservation (parotid)
  - If no CN7 deficit and dissection plane can be maintained between tumor and nerve → preserve
  - Impaired CN7 preop or if nerve branches encased or grossly involved → resect involved nerves


Management of Salivary Gland Malignancy: ASCO Guideline  Geiger, JCO 2021
Role of Postoperative RT

- Multiple studies indicate that PORT improves LRC
  - However, there are no randomized, prospective trials addressing +/- PORT
  - It is not certain if all patients would benefit
- Chen et al. (JNCCN, 2020) retrospectively reviewed 319 patients with non-metastatic ACC of the head and neck to evaluate role of PORT
  - PORT was identified as a prognostic factor for LRFS on UVA and MVA
    - Greater improvement in LRFS among pts in intermediate/high risk groups
- RT should start within 6-8 weeks of surgery
PRINCIPLES OF RADIATION THERAPY

RT: Target Volumes and Prescription

NCCN Guidelines Version 3.2021
Salivary Gland Tumors

Postoperative RT
PTV HR: 60-66 Gy @ 2Gy/fx daily
PTV SR/PTV IR: 44-50 Gy @ 2Gy/fx to 54-63 Gy @ (1.6-1.8 Gy/fx) daily

Definitive RT (or gross disease)
PTV HR: 66 @ 2 Gy/fx to 70-70.2 @ 1.8-2Gy/fx daily
PTV SR/PTV IR: 44-50 Gy @ 2Gy/fx to 54-63 Gy @ (1.6-1.8 Gy/fx) daily

• Photon, electrons, protons, or neutrons
• PTV HR includes tumor bed and/or gross disease
  – Boost > 60 Gy for adverse features, such as gross disease, positive margins, ENE
• Always cover associated nerves to at least skull base in int or low risk volume
  – Include gross PNI in high risk volume

For more details about management of PNI: See ARROCase “Head and Neck Cancers with Perineural Invasion” and the following Critical Review for more details:

IJROBP, 2018
Perineural Invasion and Perineural Tumor Spread in Head and Neck Cancer
Richard L. Bakst, MD,* Christine M. Glastonbury, MBBS,† Upen德拉 Parvathaneni, MBBS, FRANZCR, Nora Katabi, MD, Kenneth S. Hu, MD, FASTRO,* and Sue S. Yom, MD, PhD
A 47-year woman with T4N0 adenoid cystic carcinoma of the hard palate (surgery followed by adjuvant radiotherapy)
Neutron Therapy

Neutron RT may improve LRC compared with photon and/or electron beams because of

- Lower OER
- Less repair of sublethal damage (high LET radiation)
- Less variation of radiosensitivity through the cell cycle

Cost = higher toxicity
Elective Neck Management

• Elective neck dissection or irradiation is generally not indicated due to low rate of LN mets

• Special cases where elective neck management may be indicated:
  – Oral cavity or naso/oropharyngeal primary
  – Clinically suspicious nodes
  – LVSI (+)

For END:
Elective neck dissection in adenoid cystic carcinoma of head and neck: yes or no? A systematic review
Luksic, Eur Archives Oto-Rhino-Laryngo 2019

Against END:
Should a neck dissection be performed on patients with cN0 adenoid cystic carcinoma? A REFCOR propensity score matching study
Atallah, Eur J Ca 2020

In general, ENI is not recommended
Chemotherapy Remains Investigational

• Role of chemotherapy is not well-defined
  – In neither definitive nor adjuvant settings
• In palliative setting, systemic therapy is typically reserved for symptomatic patients or those with rapid progression
  – Need to weigh risks/benefits of toxicity and unknown impact on disease course, especially given indolent nature
• Concurrent chemotherapy in the primary RT setting for gross disease is our institutional preference

### Results of Phase II Trials
(recurrent/metastatic ACC)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Response Rate</th>
</tr>
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<tbody>
<tr>
<td>Apatinib</td>
<td>VEGF</td>
<td>30/65 (46.5%) with PR, no CR</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>TK</td>
<td>5/32 (15.6%) with PR, no CR</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGF</td>
<td>2/19 (11%) with PR, no CR</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>0/19 with PR/CR outside irradiated areas</td>
</tr>
</tbody>
</table>

See review by Laurie et al., Lancet Oncology 2011 for more
Future Directions: Concurrent ChemoRT?

RTOG-1008

• Randomized phase II/III trial

Resected malignant tumor of major or minor salivary gland in head/neck
  • only high grade (>30% solid component) ACC eligible
  • pT3-4 or N+ or pT1-2 N0 with close (<1mm) or microscopically positive margin
  • No gross disease
  • cM0

Adjuvant RT alone, 60-66 Gy @ 2Gy/tx (IMRT or 3DCRT photons)

Adjuvant RT, 60-66 Gy @ 2Gy/tx + weekly cisplatin (40mg/m²) x 7 doses

Primary outcome: PFS
Future Directions: Carbon Ions?

ETOILE: Randomized Carbon Ions vs Standard RT for Radioresistant Tumors

Radioresistant tumors (multiple histologies, including ACC of head/neck)

Carbon ions therapy

Photon and/or proton therapy

Primary outcome: PFS

ACCO: Adenoid Cystic Carcinoma and Carbon Only Irradiation

Randomized prospective trial

ACC of head/neck (c/pN0, M0) with an indication for RT (any of the following):
- non-operable
- R1/R2 resected
- PNI
- pT3 or pT4

Primary outcome: Freedom from loco-regional progression (@5y)

Carbon Ion Irradiation:
22 x 3 Gy (RBE)

Bimodal arm:
25 x 2Gy photon IMRT + 8 x 3 Gy(RBE) carbon ion boost

Primary outcome: PFS

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Conclusions

- Adenoid cystic carcinoma of the head and neck is a rare malignancy with an indolent course but tendency for PNI and disease recurrence (often distant mets)
- Surgical resection is the main treatment, typically followed by adjuvant radiotherapy, which improves locoregional control
  - Definitive RT is recommended when patient is not an operative candidate, surgery is too morbid, or GTR unlikely
- Particle therapy may offer improved tumor control and lower doses to OARs but currently photons/electrons are SOC
- Elective neck irradiation is generally not recommended
- The role of systemic therapy is still under investigation
References

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References


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