Mucoepidermoid Carcinoma

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Department of Otolaryngology
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Outline

- Salivary Glands
  - Anatomy
  - Masses
    - Malignant
- Mucoepidermoid Carcinoma
  - Case
  - Diagnosis
  - Associations
  - Treatment options/updates
  - Summary
Parotid Gland

- **Location:**
  - Posterior to mandibular rami split into superficial and deep lobes by the facial nerve
  - Deep lobe extends into anterior parapharyngeal space
- **Drainage:**
  - Secretes contents via Stensen’s duct which pierces the buccinator muscle prior to emptying into mouth opposite the 2nd maxillary molar
- **Blood supply:**
  - Posterior auricular a. and transverse facial a.
- **Innervation:**
  - Parasympathetics from superior salivatory nucleus $\rightarrow$ CN9 (tympanic and lesser petrosal branches) $\rightarrow$ otic ganglion $\rightarrow$ post ganglionic fibers in auriculotemporal nerve sheath (br. Of V3)
- **Claim to fame:**
  - Superficial lobe has 10-20 lymph nodes in it
  - Largest of the major salivary glands
  - “On demand” secretion of saliva
Submandibular Gland

- Location:
  - Superficial to digastric muscle, wrapping partially around posterior mylohyoid muscle

- Drainage:
  - Via Wharton’s duct emerging lateral to lingual frenulum in sublingual caruncles
  - Prior to emergence, Wharton’s duct crosses lingual nerve

- Blood supply:
  - Glandular branches of lingual and facial artery

- Innervation:
  - Direct parasympathetic innervation via superior salivatory nucleus → CN7 → chorda tympani which then runs in the sheath of the lingual nerve (Br of CN5) → submandibular ganglion → post ganglionic fibers

- Claim to fame:
  - Provides vast majority of baseline saliva
  - Over 80% of salivary stones
Submandibular Gland (picture)
Sublingual Gland

- **Location:**
  - Floor of mouth, lateral to frenulum, lateral to Wharton’s duct
- **Drainage:**
  - Via Bartholin’s ducts which drain into Wharton’s ducts
- **Blood supply:**
  - Sublingual and submental aa.
- **Innervation:**
  - Similar to submandibular gland
- **Claim to fame:**
  - Closely associated with lingual and hypoglossal nerves
  - Unencapsulated major salivary gland
Sublingual Gland (picture)
Minor Salivary Glands

- 500-1000 within the upper aerodigestive tract
  - 1-2mm in diameter each
  - Highest concentration within the hard palate
    - Most likely location of malignancy (all types) within minor salivary glands
- Minimal/no capsule
  - Higher likelihood of local invasion
- Innervation typically via facial nerve
Malignant Neoplasms of the Salivary Glands

- Rare sites of Head & Neck malignancy
  - ~3% of total number of H&N cancers
- Most occur in adults
  - 5% salivary gland malignancies occur in pediatric age group
    - Pediatric salivary gland mass much more likely to be malignant
- Not all glands have equal likelihood of malignancy
Malignant Neoplasms of the Salivary Glands

- Incidence of tumors by gland:
  - Parotid - ~73%
  - Submandibular - ~11%
  - Sublingual - ~0.5%
  - Minor Salivary - ~14%

- Percent of tumors malignant by gland:
  - Parotid - ~15%
  - Submandibular - ~37%
  - Sublingual - ~86%
  - Minor Salivary - ~46%
Malignant Neoplasms of the Salivary Glands

- Mucoepidermoid carcinoma – 34%
- Adenoid cystic carcinoma – 22%
- Adenocarcinoma – 18%
- Mixed tumors – 13%
- Acinic Cell carcinoma – 7%
- Squamous Cell carcinoma – 4%
- Et al, Anaplastic – 3%
A man walks into your clinic...

- 34y M with right sided neck mass
  - No pain
  - Noted it for the last 6 months, slowly progressive
  - No previous workup
- PMHx – “reflux” disease
- PSHx – No previous H&N surgeries
- FamHx – No cancers, +HTN
- No allergies
- SocHx – Never smoker, occasional EtOH, no drugs
- ROS – No fevers/chills, +unintentional weight loss
A man walks into your clinic...

- Physical Exam:
  - Vitals – Age appropriate/WNL
  - HEENT – Oral cavity soft, without lesions. No salivary masses noted in major glands, ~2x3cm right level 3 neck.
  - Remainder of physical exam normal
The outcome is known in this case

- Typical presentation is broad...
  - Multiple different sites to arise from leads to different presentations
- Average MEC will present:
  - 47y old
    - 8-92yo
  - Women *slightly* more likely than males
  - Painless, solitary, enlarging mass
  - ~80-90% found in parotid
    - Minor salivary gland cases favor hard palate and retromolar trigone
  - Hx of ionizing radiation exposure
- Intraoral lesions may resemble mucocele/vascular lesion early on
- ...Clearly, exceptions can be present
Many Different Faces

- May present anywhere along the aerodigestive tract
  - Bronchopulmonary sites
  - Cutaneous primary mucoepidermoid carcinoma infiltrating to parotid gland
  - Large parotid cyst in HIV patient
  - In presence of Warthins tumor
Work it up

- Workup (completed on this patient)
  - CT Neck w/ contrast
    - 2x3 cm enhancing Right level III neck mass
    - 1x2 cm central/left BOT irregularity
  - Excisional biopsy of right neck mass and direct laryngoscopy with biopsy of tongue mass
    - Malignant salivary tumor most c/w mucoepidermoid carcinoma
Typical Findings

- **Pathology**
  - Contains:
    - Epidermoid cells
    - Mucus-producing cells
    - “Intermediate” Cells
      - Predominate, form sheets/clusters
      - Modified myoepithelial cells
  - Forms multicystic spaces lined by these three cell types with solid components
  - *Keratinization rare*
Mucoepidermoid carcinoma

- H&E slide of MEC
- Multiple cell types visible
Mucoepidermoid carcinoma

- Mucin may be obvious
  - Mucicarmine, periodic acid-Schiff, Alcian blue may be used if mucinous cells scant
Grading

- Graded as either low, intermediate, or high grade
  - Intracystic component (+2).
  - Neural invasion present (+2).
  - Necrosis present (+3).
  - Mitosis ($\geq 4$ per 10 high-power field [+3]).
  - Anaplasia present (+4).
- Total point scores are 0 to 4 for low grade, 5 to 6 for intermediate grade, and 7 to 14 for high grade.
Grading

- Brandwein et al revisited the AFIP grading system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristic features</th>
<th>Defining features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Prominent goblet cell component, cyst formation intermediate cells may be prominent</td>
<td>Lack of grade III defining features, lack of aggressive invasion pattern</td>
</tr>
<tr>
<td></td>
<td>circumscribed growth pattern</td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>Intermediate cells predominate over mucinous cells mostly solid tumor squamous cell</td>
<td>Aggressive invasion pattern, lack of grade III defining features</td>
</tr>
<tr>
<td></td>
<td>may be seen</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>Squamous cells predominate intermediate and mucinous cells must also be present mostly</td>
<td>Necrosis perineural spread vascular invasion bony invasion &gt;4 mitoses/10 HPF</td>
</tr>
<tr>
<td></td>
<td>solid</td>
<td>high-grade nuclear pleomorphism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracystic component &lt;25%</td>
<td>2</td>
</tr>
<tr>
<td>Tumor front invades in small nests and islands</td>
<td>2</td>
</tr>
<tr>
<td>Pronounced nuclear atypia</td>
<td>2</td>
</tr>
<tr>
<td>Lymphatic and or vascular invasion</td>
<td>3</td>
</tr>
<tr>
<td>Bony invasion</td>
<td>3</td>
</tr>
<tr>
<td>&gt;4 mitoses/10 HPF</td>
<td>3</td>
</tr>
<tr>
<td>Perineural spread</td>
<td>3</td>
</tr>
<tr>
<td>Necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>2-3</td>
</tr>
<tr>
<td>Grade III</td>
<td>4 or more</td>
</tr>
</tbody>
</table>
Grading

- Low grade lesions, Grade I
  - Prominent cystic component
  - Well differentiated cells
  - Low mitotic activity
  - Low atypia

- Similar to:
Grading

- High grade lesions, Grade III
  - Opposite of low grade lesion
Grading

- Intermediate lesions, Grade II
  - Not low and not high, but features of both
Grading

- A SEER database study by Chen et al in 2014
  - 2400 patients
    - 522 low grade
    - 1137 Intermediate
    - 741 High grade
  - Tumor grade (mostly AFIP) correlated with disease specific survival HR of 14.9
    - Additional factors correlating with decreased DSS
      - Tumor size >4cm (HR 12.02), Distant Mets (HR 10.79), Extraparenchymal extension (HR 6.96)
Workup

Done:
- CT Neck
- Excisional bx neck mass
  - Path indicative of high grade MEC
- Bx tongue lesion
  - Path similar to neck mass
- Margins positive

To do:
- Other imaging?
- Why no FNA?
- Treatment?
Imaging

- Common findings:
  - CT with contrast
    - Low grade:
      - Well circumscribed mass with cystic features
      - Solid portions enhance
      - Rare calcifications
Imaging

- Common findings:
  - CT with contrast
    - High grade:
      - Poorly defined lesion
      - Infiltrate locally
      - Appear solid
Q

Typical signal intensities on MRI for a low grade mucoepidermoid carcinoma are:

a) T1 High, T2 High
b) T1 High, T2 Low
c) T1 Low, T2 High
d) T1 Low, T2 Low
Typical signal intensities on MRI for a low grade mucoepidermoid carcinoma are:

a) T1 High, T2 High
b) T1 High, T2 Low
c) T1 Low, T2 High
d) T1 Low, T2 Low
Imaging

- MRI
  - GENERALLY-
    - Benign epithelial masses and low-grade malignancies:
      - Low T1 signal
      - High T2 signal
    - High grade carcinomas:
      - Low-intermediate T1
      - Low-intermediate T2
  - Gadolinium useful adjunct
MRI – Low Grade MEC

(A) T2                     (B) T1               (C) T1 Fat suppressed
MRI – High Grade MEC

- (A) T₂, (B) T₁
  - Note both have somewhat low signal intensity
Imaging as a diagnostic modality

- Studies are split as to the utility of MRI in determining malignant vs benign masses
  - Som et al – 35 patients
    - Low grade – Low T1, High T2
    - High grade – Low T1, Low T2 with poorly defined margins
  - Freling et al – 116 patients
    - No correlation between signal intensity, tumor grade
    - Only able to determine malignancy with evidence of invasion to adjacent structures
  - Kashiwagi et al – 20 patients with MEC
    - 5 high, 3 intermediate, 12 low
    - Believe that their findings correlate well with histologic findings
Bottom Line

- MRI useful for determining extent of disease
- MRI cannot be trusted to solely determine benign vs malignant disease
That being said ...

- Patient received an MRI to assess for extent of tumor invasion
  - Left image - T1 with gadolinium
  - Right image – T1
Case MRI (continued)

- Sagittal
  - Left image T1
  - Right image T2
What about the primary lesion?

- Nondescript. The neck nodes were more impressive.
PET/CT

- Tumor grade and tumor stage
  - Important prognostic and treatment ramifications
  - Considered in tandem
  - MEC has capacity to have distant metastasis
    - High grade (~3%) > low (~0.2%)
  - High likelihood of nodal mets
    - High grade (~57%) > low (~11%)
  - PET/CT shown to be advantageous in workup of salivary malignancy
FNA?

- Generally viewed as a good first step in workup of a neck mass
- However...
  - Limited use in salivary malignancy
    - Many salivary tumors can only be diagnosed with the growth pattern; not just cell types
  - High rate of error
    - Sensitivity lower than specificity
    - Common to misdiagnose a malignant lesion as benign
    - False negative rate – 32% overall
- FNA MEC
  - Mixture of cell types
  - False negative rate for MEC – 43% (low grade lesions)
    - Has since been refuted somewhat in the literature with lower FN rates
FNA?

• Conclusion
  • Has been identified as a useful diagnostic tool with some disparity within the research
  • Predictive value of a negative FNA is low and should not supersede clinical suspicion
Causes

- Definitive cause/changes in mucoepidermoid carcinoma elusive
  - Common translocation in salivary and bronchial MEC: \( t(11;19)(q21;p13) \)
    - Found in as high as 81% MEC
    - Exon at MECT1 (19p13) with unknown purpose meets with exon at MAML2 (11q21)
  - In vitro administration of suppressing test substances successful in slowing growth of cell lines
    - MECT1-MAML2 demonstrates predilection to less aggressive MEC
      - Additionally found in Warthin’s tumor and some acute leukemias
Causes?

- HPV?
  - Brandwein et al. 2012 noted transcriptionally active HPV strains 16/18 in cases of MEC
    - Noted that it has a common incidence
    - E6 viral oncogene and HPV DNA isolated within tumor cells
    - Presence does not indicate causation
Treatment

- Traditional treatment has always included surgical excision
  - Differences in Low vs High grade?
    - Numerous papers have demonstrated that survival characteristics have been linked to grade
  - Staging remains key
# Treatment - Staging

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor =2cm in greatest dimension without extraparenchymal extension (clinical or macroscopic evidence of invasion of the soft tissues, not microscopic evidence)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2cm but not more than 4cm in greatest dimension without extraparenchymal extension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;4cm and/or tumor has extraparenchymal extension</td>
</tr>
</tbody>
</table>
| T4a               | Moderately advanced disease  
  - Tumor invades the skin, mandible, ear canal, and/or facial nerve |
| T4b               | Very advanced disease  
  - Tumor invades skull base and/or pterygoid plates and/or encases carotid artery |
# Treatment - Staging

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node $\geq 3$cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node $&gt;3$cm but not more than $6$cm in greatest dimension; or in multiple ipsilateral lymph nodes, none $&gt;6$cm in greatest dimension; or in bilateral or contralateral lymph nodes, none $&gt;6$cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node $&gt;3$cm but not more than $6$cm in greatest dimension</td>
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<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none $&gt;6$cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none $&gt;6$cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node $&gt;6$cm in greatest dimension</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**Distant metastasis (M)**
## Treatment - Staging

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<thead>
<tr>
<th></th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
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<tbody>
<tr>
<td>I</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>III</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
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<tr>
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<td>N1</td>
<td>M0</td>
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<td>T3</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td>IVA</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td></td>
<td>T4a</td>
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<td>IVC</td>
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<td>N Any</td>
<td>M1</td>
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## Treatment - Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>T1</td>
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<td>M0</td>
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<tr>
<td>II</td>
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<td>N0</td>
<td>M0</td>
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<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IVA</td>
<td>T4a</td>
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<td>T4a</td>
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<td>IVB</td>
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<td>T4b</td>
<td>N Any</td>
<td>M0</td>
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<tr>
<td>IVC</td>
<td>T Any</td>
<td>N Any</td>
<td>M1</td>
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<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year Relative Survival Rate</th>
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<tbody>
<tr>
<td>I</td>
<td>91%</td>
</tr>
<tr>
<td>II</td>
<td>75%</td>
</tr>
<tr>
<td>III</td>
<td>65%</td>
</tr>
<tr>
<td>IV</td>
<td>39%</td>
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</table>
So... how is it treated?

- **Low grade tumors**
  - Surgical excision for local control
    - If parotid origin, often will not require sacrificing facial nerve if not within tumor

- **High grade tumors**
  - Behave more like squamous cell carcinoma
    - Surgical excision of primary lesion
    - Neck dissections if nodal disease
    - Adjuvant radiation

- Thus far, chemotherapy has not been shown to have a role in the treatment of salivary gland malignancy
Treatment

- Intermediate grade tumor:
  - Treatment less clear
  - Higher predilection for nodal disease than low grade
  - Local behavior more similar to low grade than high grade
  - No consensus view
  - Due to possibility of nodal mets, often treatment favors more aggressive approach
Elective Neck Dissection (END)?

- Salivary malignancy has high risk of occult nodal metastasis
  - Nobis et al examined benefit of elective neck dissection in patients with clinically negative necks in salivary primary tumors of all types and origins
    - Overall rate of +nodes following END: 39.1%
    - MEC specific rate: ~40%
      - Of these those with low-grade MEC had 0 patients with occult nodal neck disease
  - Site specificity to nodal metastasis
    - *Submandibular gland* more likely than hard palate salivary glands to produce +nodes
Elective Neck Dissection

• Results from Nobis mirror those from several other studies:
  • Armstrong et al, Zbaren et al, Stennert et al, Spiro et al
    • All of the above recommend neck dissection at excision of primary tumor
  • Regional recurrence ≤5% when ND or radiation had been performed (Valstar et al)
Recurrence/Survival

- Only a few studies have been done specifically on MEC
  - Brandwein et al

![Graph 1: Disease-free survival (months) for all patients (n = 48) versus histologic grade.](image1)

![Graph 2: Disease-free survival (months) for all patients (n = 48) versus collapsed stage (I/II vs III/IV).](image2)
Pediatric MEC

- They are like little adults with the exception of:
  - 50% salivary gland masses malignant
    - Overall incidence remains low: only 5% total MEC in childhood
    - Seldom prior to age 10y

- Overall prognosis good
  - Study from MD Anderson
  - 10y overall survival of 94%

- Treatment very similar
  - Surgery for initial control +/- ND
  - Adjuvant radiotherapy
In our patient

- Given PET avidity in base of tongue and tonsil beds
  - Transoral robotic surgery for removal of suspected primary lesion
- Given Bilateral nodal dx
  - Underwent bilateral neck dissection
- Given High grade
  - Adjuvant radiotherapy

- Aggressive disease, with local recurrence requiring reexcision
Q

A patient walks in with the lesion seen here. What is the correct diagnosis?

a) Mucoepidermoid carcinoma
b) Squamous cell carcinoma
c) Necrotizing sialometaplasia
d) Cigarette burn
Q

A patient walks in with the lesion seen here. What is the correct diagnosis?

a) Mucoepidermoid carcinoma
b) Squamous cell carcinoma
c) Necrotizing sialometaplasia
d) Cigarette burn
The Pretender(s)

- Necrotizing Sialometaplasia is an oral lesion than looks frankly malignant
  - History typically includes some sort of trauma
    - Traumatic intubation, perhaps?
  - Necrosis of salivary tissue following ischemia
  - Location typically hard palate
    - Typically minor salivary glands
  - Treatment = do nothing, once diagnosis is certain
    - Resolves in a matter of weeks
- Numerous oral lesions may look similar early in their course
Mucoepidermoid carcinoma (MEC)
  - Most commonly in parotid
    - Next most often Minor salivary glands, then submandibular gland
  - Most common **primary malignancy** of parotid gland in adults and pediatric population
  - High grade---low grade, depends on ratio of mucinous cells to epidermoid cells
    - Grading and staging paramount in determination of treatment and prognosis
    - Low grade lesions may be treated with surgical excision
    - High grade lesions require local excision, would benefit from elective neck dissection in N-o necks, and possible adjuvant radiation
    - **NO CONSENSUS VIEW ON TREATMENT PROTOCOL**
  - Pediatric population treated similarly to adults with good overall survival
  - MRI useful in establishing extend of disease, may be of some benefit in grading lesion
  - FNA has mixed utility in literature
Thank you Dr. Darling for that excellent discussion of mucoepidermoid carcinoma. I think we all have taken some part in the care of this kind. I think one important thing about his initial staging and probably the most ominous initial thing was that his neck disease was contralateral to his primary, although it wasn’t until later in the workup that with the imaging we were later to identify the primary lesion in the contralateral side of the neck. So he was NTC to start out with, and I believe he has failed not in that neck but in the ipsilateral neck. He’s undergoing palliative chemotherapy with very little evidence-base, but that’s the option that he has remaining at this point.

I think that your final discussion of the pretenders is really important, especially of the hard and soft palate. The morbidity of an operation or even an unnecessary large biopsy in this area is pretty high. In addition to necrotizing metaplasia some of the infections like tb and histo and blasto can also cause bad looking lesions like that. And you know, psuedoepithelial hyperplasia, though more common on the tongue, can also appear on the palate.

I will end by quoting Dr. Quinn, “Do anything you want to it for a month, but then you have to biopsy it.” Steroids, antibiotics, observation, magic, then biopsy.


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