Mucoepidermoid carcinoma (MEC) remains the most common type of salivary gland malignancy, with a histopathology which is uniquely its own. A full understanding of the salivary glands and the various types of salivary masses can aid in the understanding of its behavior, clinical picture, and its eventual treatment course outcomes.

Salivary gland tumors remain an uncommon source of head and neck malignancy with MEC having an incidence of approximately 3/1,000,000 people with slightly higher predilection in males. These tumors are unique in that the determination of a patient’s prognosis has not only to do with the staging of the tumor, but also the histological grade. Low grade (grade I) lesions have a behavior completely different than those of high grade (grade III) MEC with corresponding changes in the treatment course required for adequate control of the disease. Surgery remains the most common treatment, but adjuncts may be required depending on tumor grade.

SALIVARY GLAND ANATOMY:

There are 3 paired sets of major salivary glands and numerous minor salivary glands present within the upper aerodigestive tract; each have their own unique innervations, behaviors and other defining characteristics. These are:

1) Parotid gland
2) Submandibular gland
3) Sublingual Gland

Parotid Gland:

These paired glands are located posterior to mandibular rami split into superficial and deep lobes by the facial nerve bilaterally. They are the largest of the major salivary glands. The deep lobe extends into anterior parapharyngeal space and in fact forms the part of the lateral border of this deep neck space. It secretes contents via Stensen’s duct which pierces the buccinator muscle prior to
emptying into mouth opposite the 2nd maxillary molar. Occasionally, the angle formed when the duct pierces through the muscle can be acute enough to form a stricture causing obstruction and buildup of saliva within the duct and gland. Though uncommon, this situation is unique to the parotid glands. The gland secretes an “on demand” salivary load and provides the majority of saliva during mastication. The gland is instructed to do so via parasympathetics from the superior salivatory nucleus which travel through the glossopharyngeal nerve (typanic and lesser petrosal branches) before synapsing on the otic ganglion. The postganglionic fibers travel through the auriculotemporal nerve sheath which is a branch of the mandibular nerve (V3). Of note, the parotid gland is the only salivary gland to contain lymph nodes, as there are between 10-20 found in the superficial lobe.

**Submandibular Gland:**

These paired glands are located superficial to digastric muscle, wrapping partially around posterior mylohyoid muscle. These glands provide the vast majority of the baseline saliva secretion, but also over 80% of salivary stones. They drain via Wharton’s duct which emerges lateral to lingual frenulum in sublingual caruncles. Prior to emergence, Wharton’s duct crosses lingual nerve superiorly which is an important surgical landmark in level 1 neck dissections. The gland is instructed to secrete direct parasympathetic innervation starting in the superior salivatory nucleus which sends fibers through the facial nerve via the chorda tympani which then travels within the nerve sheath of the lingual nerve. These fibers synapse on the submandibular ganglion which provides the post ganglionic fibers which stimulate the gland. The fibers are robust enough that the submandibular ganglion and its post ganglionic fibers must be purposely severed in order to remove the gland.

**Sublingual Gland:**

These are the smallest of the major salivary glands and, as such, are unique in the distinction that they are the only major salivary glands which are not encapsulated. They are located in the floor of mouth, lateral to frenulum, lateral to Wharton’s duct, and closely related with the lingual and hypoglossal nerves. They drain via numerous small ducts named the ducts of Rivinus. The largest of these ducts is the sublingual duct (of Bartholin) which in turn drains into Wharton’s duct. It is instructed to secrete saliva in much the same way as the submandibular duct and also contributes to a person’s baseline.

**Minor Salivary Glands:**

There are between 500 and 1000 spread throughout the upper aerodigestive tract. Each gland is roughly 1-2 mm across in the largest dimension. Within the aerodigestive tract, there are a number of areas with higher concentrations of minor salivary glands. Most notably, the hard palate has a disproportionate number of minor salivary glands which, unsurprisingly, makes this the most likely location for a minor salivary gland malignancy. Like the sublingual glands, they have no capsule to speak of which increases the likelihood of local tumor invasion.

Each of these salivary glands is susceptible to tumors and malignancy; however, the incidence within these glands differs. For instance, the parotid gland is the most likely to harbor a tumor (benign or malignant); containing 73% of salivary gland tumors compared to the sublingual glands which only contain ~0.5% of salivary gland tumors. However, parotid tumors are the least likely to be malignant with only 15% of parotid tumors being malignant. Compare that to the sublingual gland, in which a
tumor is malignant 86% of the time. The proportion of salivary tumors that are malignant roughly corresponds to the proportion of mucinous:serous saliva. The parotid gland is the most serous followed by submandibular followed by sublingual, which has the highest proportion of mucinous secretion. Based solely on the volume of tumors; however, the parotid gland is still the most likely salivary gland to harbor a primary malignancy which is to say nothing of the possibility of metastasis of a separate malignancy to the parotid lymph nodes.

Of the potential salivary gland malignancies, mucoepidermoid carcinoma (MEC) is the most common by a significant margin. Roughly 34% of all salivary malignancies are MEC, versus 22% adenoid cystic carcinoma, and 18% adenocarcinoma. Squamous cell carcinomas are much less common within the salivary glands, making up roughly 4% of all salivary gland malignancies. It should come as no surprise then, that a complete understanding of MEC is important in the workup and treatment of salivary tumors.

**PRESENTATION:**

The typical presentation of mucoepidermoid carcinoma (MEC) is broad, owing to the fact that it can arise from any site of salivary tissue, leading to numerous possible sites of origin and numerous presenting symptoms. However, the most common MEC patient will be ~47y male as they are slightly more likely to have MEC than females. It is important to note however, that the gap between male and female incidence of this cancer is narrower than in most. It presents as a single, painless, enlarging mass present anywhere over the aerodigestive tract; however, over 80% are found within the parotid gland. If it were to originate from a minor salivary gland it is most likely to favor the hard palate or retromolar trigone as these sites have the highest concentration of minor salivary glands.

Unfortunately, its appearance on initial presentation may resemble a vascular lesion, mucocele or other benign mass, thus it underscores how important follow up is for any oral cavity lesion. However, it is important to note that these tumors are not limited to the oral cavity or the oropharynx. There have been case reports of a cutaneous primary of MEC infiltrating into the parotid gland, a large parotid cyst in the setting of a patient with HIV, or in the presence of a concurrent Warthin’s tumor. All such presentations are atypical and decrease ones suspicion of MEC. Additionally, there are a significant amount of bronchopulmonary mucoepidermoid carcinoma which has been studied extensively. Their histopathology is similar to those of the head and neck, but full discussion regarding their workup and treatment is beyond the scope of this chapter.

**CAUSE:**

The definitive cause for MEC remains elusive at present time; however, a common gene translocation at t(11;19)(q21;p13) has been found in approximately 81% of MEC tumors studied. This segment encodes a CREB (cAMP response element-binding protein) which is a transcription factor; the downstream purpose of which is also largely unknown. A similar translocation is often found in Warthins tumors and certain leukemias. Additionally there has been a causal link implicated in recent research with cytomegalovirus, as well as the presence of HPV DNA in a large proportion of the tumor cells. Though, a definitive link has yet to be established in both cases.
**WORKUP:**

As is often the case, the workup should begin with a complete history and comprehensive head and neck exam. After eliciting a history that raises your suspicion for MEC, workup should involve tissue diagnosis at the primary site, or if unknown, often at the site of regional metastasis. Owing to the extremely variable nature of the presentation, as well as, the behavior of the disease, this process may not be as cut and dry as it is with an oral cavity lesion suspicious for squamous cell carcinoma.

Lesions within minor salivary glands may initially manifest with an appearance resembling a benign mass such as a mucocele. Thus, observation initially may be opted for; however, this demonstrates exactly how important it is to ensure adequate follow up for all head and neck lesions as one can never be exactly certain that a lesion is benign. Eventually, a tissue biopsy will be required given the steady enlargement of the lesion which is especially important in MEC because the histologic classification of the disease is paramount in determining the treatment course that the patient will endure.

**Histology:**

Typical findings on pathologic sectioning will demonstrate multiple cell types. Chiefly 1) epidermoid cells and 2) mucus producing cells, which when combined illustrate the reason this tumor is so named. There is, additionally, an “intermediate” cell type which typically predominates. These are theorized to be modified epithelial cells. If these cell types are present the pathologist would have high suspicion that the lesion is a mucoepidermoid carcinoma on an FNA. If an open/excisional biopsy is undertaken the architecture of the tumor can be visualized as these cell types are arranged lining several multicystic spaces with solid components within the same tumor mass. Keratinization is rare and immunohistochemistry is essentially unhelpful in determining a diagnosis in these cases. Typically the mucin containing cells are obvious on simple H&E staining; however, if the sample in question contains relatively few of the mucin producing cells, a mucicarmine, periodic acid-Schiff, or alcian blue stain may be used to better identify them.

Obtaining a sample adequate to view the architecture of the tumor is ideal and FNA, whereas it is a fine first step in the evaluation of oral lesion or neck mass, it has a very limited role in salivary malignancy. Many salivary tumors can only be identified by viewing the growth pattern, and not just the presence of certain cell types. Thus, there is a high rate of error if used as the sole method of diagnosis. The sensitivity is lower than the specificity and easier to misdiagnose a malignant lesion as benign. The overall false negative rate for FNA diagnosis of salivary gland malignancy is approximately 32% and it is even higher for MEC at roughly 43%; though this is chiefly with lower grade lesions. This assertion has

![Figure 1: H&E stain of salivary tumor. 3 distinct cell types are present with a large cystic cavity; typical of the tumor architecture in low grade mucoepidermoid carcinoma](image-url)
been refuted somewhat recently in the literature with a number of sources citing lower false negative rates in their own experiences. Thus, FNA is a useful diagnostic tool, however due to the low predictive value of a negative FNA, it should never supersede a clinicians’ suspicion.

Obtaining a tissue sample which contains the growth pattern is especially important in MEC as this will be used to help determine the relative aggression and prognosis of the patient’s disease. Not all MECs are created equal and there are a number of adopted grading systems in use to classify these tumors. One of the most widely used is that devised by the Brandwein group as a revision of the system created by the Armed Forces Institute of Pathology. The Brandwein group lobbied to change the criteria because they felt the original AFIP system was not strict enough and that these tumors should be treated more aggressively to obtain better survival rates. Each grading system identifies various characteristics of the sample and reduces these to a numerical score which correlates to a specific tumor grade. Grade I lesions are the least aggressive and most likely to act locally and grade III lesions are the most aggressive. Grade II lesions fall in the intermediate range and will have characteristics of both.

**Tumor Grading:**

The Brandwein classification system is seen below:

- Intracystic component <25% 2 points Grade I - <2 points
- Tumor front invades in small nests/Islands 2 points Grade II – 2-3 points
- Pronounced nuclear atypia 2 points Grade III - >4 points
- Lymphatic/vascular invasion 3 points
- Bony Invasion 3 points
- >4 mitosis/10 HPF 3 points
- Perineural spread 3 points
- Necrosis 3 points

From the above one can see that an MEC without the signs of aggression will be graded lower; however, it only takes 1-2 of the above items to upgrade the tumor to a grade III which has far reaching effects in behavior and treatment, as well as, prognosis. A SEER database study reviewed 2400 patients with MEC and found that tumor grade (using AFIP grading system mostly) was the defining factor when correlated with disease specific survival (Hazard ratio 14.9). Other important factors correlating strongly with disease specific survival were tumor size >4cm (HR 12.02), presence of distant metastases (HR 10.79), and extraparenchymal extension (HR 6.96). These items are typically what contributes to the stage of a tumor and it should be noted that tumor grade was as important, if not more important when determining prognosis.

**Imaging:**

As a part of the workup in any head and neck lesion with concern for malignancy, imaging plays a vital role. The case of mucoepidermoid carcinoma is no different. Upon obtaining a tissue diagnosis, or having suitable clinical suspicion, imaging of the head and neck is recommended. Owing to the relative paucity of salivary gland tumors, let alone mucoepidermoid carcinomas, no strict imaging
protocol as yet exists. However, the general agreement in the literature is that a CT Neck with/without contrast is a useful study to evaluate staging.

Findings on a CT scan for mucoepidermoid carcinoma vary depending on the grade of the tumor. A low grade tumor will have larger cystic components, lesser solid components, and rare calcifications. Thus when viewed on a CT scan, the appearance of a grade I lesion will be that of a well circumscribed mass with cystic features, the solid portions of the tumor will enhance readily. Conversely, a grade III lesion will be poorly circumscribed, with local infiltration and have a solid appearance. Grade II lesions are intermediate and will generally have a combination of traits which is difficult to classify. The only clue as to the etiology of the mass will be the location if present within salivary tissue. See the images in figure 2 below for the typical appearance on CT scan.

Figure 2: Left image is CT with contrast of grade I MEC in right parotid gland, note cystic component. Right image is a grade III MEC of the left base of tongue, note the irregular borders and absence of cystic component.

An MRI is often obtained to better clarify the soft tissue characteristics of the tumor and determine if any gross perineural invasion is present. Generally, grade I MEC will have low T1 signal and high T2 signal owing to the higher cystic component. Whereas a grade III MEC will have low T1 and T2 signal. Gadolinium contrast is a useful adjunct to identify malignant tissues as they will readily enhance. See Figure 3 below for the typical appearance of low and high grade MEC. There are those who have sought to prove that one could use the MRI to identify malignant vs more benign lesions in these cases. The studies are split though the largest series in the literature was unable to find any statistically significant correlation between the MRI grading estimate and the histologic findings and as such, is an interesting academic exercise, but obviously cannot be trusted as the sole means of classification.
PET/CT has a rapidly increasing role in the staging workup of salivary gland malignancies. Increased avidity in regional sites carries important prognostic and treatment ramifications as MEC has the capacity to have distant metastases (3% in grade III vs ~0.2% in grade I) and has a high likelihood of nodal metastases (57% in grade III vs 11% in grade I).
A patient with a grade I MEC may often undergo primary surgical excision of the lesion with very good outcomes. If the primary lesion is within the parotid and facial nerve function is intact, the nerve may typically be dissected free and preserved. Few studies have been carried out regarding the treatment of mucoepidermoid carcinoma and thus, no rigid treatment protocol exists. However, one of the largest studies on the topic looked at disease free survival as it relates to grade and staging and found that the disease free survival was >95% for grade I lesions 2 years s/p surgical excision. Unfortunately, grade III lesions behave more similarly to squamous cell cancers with a recommended treatment course to reflect that increased tumor aggression.

A patient with a grade III MEC will seldom undergo only surgical excision. As of this time, chemotherapy has not been shown to have a role in the treatment of salivary malignancy, and very little work has been done regarding radiation therapy as the sole means of treatment owing to the fact that it is difficult to obtain a statistically significant number of cases for comparison. In the case of higher grade MEC, often the treatment course involves primary surgical excision with definite neck dissection if nodal disease present, and adjuvant radiation.

One of the main questions regarding treatment is when to perform a neck dissection. When examining the pathology from patients with clinically N0 necks, the overall rate of nodal disease was actually 40% in patients with high grade MEC. This number dropped to 0% with grade I tumors. Using this information, the consensus view within the literature is to perform an ipsilateral elective neck dissection at the time of primary tumor excision when the primary lesion is thought to be higher grade and certainly once definitive pathologic confirmation of grade II or grade III MEC is obtained. Grade II disease is included with grade III owing to their predilection for nodal metastasis. The typical extent of the neck dissection was a supraomohyoid dissection (levels 1-3) with completion of a full selective neck dissection (1-5) if frozen sections demonstrated disease. Adjuvant radiation therapy may be used for greater control of high grade tumors similar to its use with treatment of squamous cell carcinoma.

Despite an appropriately aggressive treatment course, high grade and high stage tumors demonstrate a poor disease free survival rate. When examining DFS on the basis of grade only, the 10 year rates are <30%.

**Pediatric Population:**

Despite the increased percentage of malignancy found in pediatric salivary masses, the overall prognosis is positive with overall survival rates of up to 94% averaged across all stages and tumor grades. The treatment of these tumors is identical to the described treatment courses for adult patients as the disease process appears identical. The largest study in the pediatric population was out of the MD Anderson Cancer Center and utilized surgery for initial control with appropriate elective neck dissections depending on grade, with the addition of adjuvant radiotherapy for high grade lesions.

**CONCLUSION:**

Mucoepidermoid carcinoma is the most common salivary malignancy in the adult and pediatric population with a unique pathophysiology. The prognosis hinges greatly on not only the tumor stage, but also the histologic grade of the lesion. Typical treatment involves surgical excision for low grade
lesions; however, in higher grade lesions, the recommended treatment is surgical excision with elective neck dissection in the ipsilateral neck followed by adjuvant radiation therapy. Grade II tumors are treated similarly to grade III since, even though they tend to behave locally more similarly to grade I tumors, they possess a predilection for nodal metastasis like grade III. Definitive work up and treatment protocols have not been developed due to the relative paucity of MEC case to power research. Work is ongoing regarding the determination of a causal etiology which may allow for more targeted therapies including chemotherapeutic agents which, at present time, have no major role to play in the treatment of this disease.

**FACULTY DISCUSSION: VICENTE RESTO, MD, PHD, FACS, CHAIR**

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.

**SOURCES:**

• Tryggvason et al. Accuracy of fine-needle aspiration and imaging in the preoperative workup of salivary gland mass lesions treated surgically. Laryngoscope. 2013 Jan;122(1):158-163
• Special thanks to Cumming’s Otolaryngology, Radiopaedia, American Cancer Association, and the Atlas of Genetics and Cytogenetics in Oncology and Haematology

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