

**TITLE: Current controversies in the Management of Malignant Parotid Tumors**

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Given the remarkable advances during the last decade in our understanding of tumor biology, intracellular ultrastructural aberrations, imaging, radiotherapy delivery and the synergism of radiotherapy when used with chemotherapy, we continue to experience areas of controversy in the management of primary parotid neoplasms. There are several contributing factors as to why there are no clear answers in certain clinical situations. Chief among these factors is the rarity and multiple histological subtypes that exist in parotid neoplasms. In addition many of these tumors are slow growing and require long observation times. To be discussed in this article are the following controversies: The utility of FNA biopsy, imaging modalities, MRI compared to CT and PET, usefulness of post-operative radiotherapy, facial nerve management and elective neck dissection to manage N0 neck.

## **General**

Malignant parotid neoplasms represent roughly 1-3% of all head and neck malignancies. Recurrence of these neoplasms often indicates aggressive disease which may ultimately be difficult to treat, and may predict future therapeutic failure. It is therefore important to attempt to recognize aggressive features initially to prevent recurrence. Factors such as tumor stage, facial nerve involvement, neck disease and histologic grade are amongst the most important to assess.

## **History of Salivary Gland Tumors**

In 1648 Riolan identified the glandular substance of parotid and Neils Stenson then identified the parotid duct in sheep in 1660. However it wasn't until 1825 when Heyfelder avoided the facial nerve during a parotidectomy. This was preceded by the successful identification of the trunk of the facial nerve by Velpeau in 1830. Bell and Velpeau determined the facial nerve was responsible for facial animation. They determined facial sensation was from CN V.

## **Anatomy**

The parotid gland is the largest salivary gland. The parotid duct lies on an imaginary line between the external nares and the tragus of the ear. Boundaries of the parotid gland are

described as such: external auditory canal, ramus of mandible, & mastoid process. The gland is encased in a sheath which is continuous with the SMAS and the musculature of the face. Stensen's duct courses anterior to masseter muscle, transverses the buccinator, and exits orally along maxillary second molar. An artificial division is created embryologically between the deep and superficial lobes by facial nerve.

The facial nerve exits from stylomastoid foramen and then divides into temporofacial and cervicofacial. Its terminal branches are Temporal/Frontal, Zygomatico-orbital, Buccal, Mandibular, and Cervical. In order to help find the facial nerve during a parotidectomy, several key landmarks have been described by various authors. Among the most useful are the tympanomastoid suture, the digastrics and the tragal pointer. The trunk of the facial nerve can be identified 1cm deep and inferior to the tragal pointer. Additionally the nerve is known to be lateral to the styloid process and superficial to the retromandibular vein. If the tumor makes it difficult to identify the main trunk, a retrograde dissection can help to find the nerve as well.

## Histology

Mucoepidermoid carcinoma is the most common malignant neoplasm of the parotid gland and the second most common malignant tumor of the submandibular gland. It constitutes approximately 30% of all malignant tumors of the salivary glands.

Mucoepidermoid carcinomas are usually classified as low-grade or high-grade tumors. However, some authors also include an intermediate-grade as well. Low-grade tumors have a higher proportion of mucous cells to epidermoid cells. These lesions behave more like benign neoplasms but are still nevertheless capable of local invasion and metastasis. High-grade mucoepidermoid carcinomas have a higher proportion of epidermoid cells, and it may be difficult to differentiate this entity from squamous cell carcinoma. High-grade tumors are aggressive neoplasms with a high propensity for metastasis.

Low-grade tumors are usually small and partially encapsulated. High-grade neoplasms are usually larger and locally invasive. On cut sections, low-grade mucoepidermoid carcinoma may contain mucinous fluid, whereas high-grade tumors are solid. Microscopically, low-grade mucoepidermoid carcinoma demonstrates aggregates of mucoid cells separated by strands of epidermal cells. High-grade tumors have few mucoid elements and the epidermoid cells predominate.

Adenoid cystic carcinoma accounts for approximately 10% of all salivary gland neoplasms. It is the second most common malignancy of the parotid glands but is the most common malignancy of the submandibular and minor salivary glands. Adenoid cystic carcinoma occurs with equal frequency in men and women, usually in the fifth decade of life. Facial paralysis and pain occur as initial symptoms in a small fraction of cases.

Adenoid cystic carcinoma has a contradictory clinical course. The tumor is slow growing, but its clinical course is relentless. Multiple local recurrences can occur despite adequate surgical intervention and although regional metastatic spread is uncommon, distant spread to the lungs and bones are frequent.

Grossly, the tumor is usually monolobular and either nonencapsulated or partially encapsulated. The mass often demonstrates infiltration of surrounding normal tissue.

Microscopically, adenoid cystic carcinoma has a basaloid epithelium arranged in cylindrical formations in an eosinophilic hyaline stroma. Different histologic patterns have been identified, including cribriform, solid, cylindromatous, and tubular. The solid histologic pattern appears to have a worse prognosis in terms of distant metastases and long-term survival.

Perineural invasion is a typical feature of adenoid cystic carcinoma. This explains the difficulty in tumor eradication despite the appearance of complete tumor removal. Complete surgical excision and postoperative radiation therapy is recommended for the management of this tumor. For select small tumors that are completely excised, however, postoperative radiation therapy may be withheld. There is also growing evidence that fast neutron radiotherapy may be more effective than conventional photon radiation for adenoid cystic carcinoma. Long-term follow-up is mandatory for these patients because of the slow, relentless disease progression.

Acinic cell carcinomas comprise 5% to 11% of all salivary gland cancers. The vast majority occur in the parotid gland. It affects females more often than males and occurs in the fourth to sixth decade of life. The tumor can be multicentric in 2% to 5% of cases and it ranks behind Warthin's tumor for the frequency of bilateral parotid involvement.

Grossly, the well-circumscribed tumors often have a fibrous capsule. There are two populations of cells: those resembling serous acinar cells of the salivary gland and those with a clear cytoplasm. Tumors occur in several configurations, including cystic, papillary, vacuolated, or follicular. There is often a lymphoid infiltrate, and cells are characteristically positive on periodic acid–Schiff staining.

Adenocarcinoma most commonly occurs in the minor salivary glands, followed by the parotid gland. This neoplasm represents approximately 15% of malignant parotid neoplasms. Adenocarcinomas occur equally in both sexes and usually present as a palpable mass. They behave aggressively with a strong propensity to recur and metastasize.

Grossly, adenocarcinoma is firm or hard and attached to the surrounding tissue. Microscopically, the cylindrical cells of variable height form papillae, acini, or solid masses. Most neoplasms produce mucus, which can be detected by mucicarmine stain. Adenocarcinoma can be differentiated from mucoepidermoid carcinoma by the lack of keratin staining. The degree of glandular formation has been used as a means of grading these tumors.

Squamous cell carcinoma of the salivary glands represents a rare neoplasm that constitutes 0.3% to 1.5% of salivary gland tumors. This malignancy occurs more often in the submandibular gland than the parotid gland. Proper diagnosis of squamous cell carcinoma requires exclusion of contiguous spread of a squamous cell carcinoma into the gland, metastases to the gland, and high-grade mucoepidermoid carcinoma.

These tumors usually present as firm indurated masses and occur more commonly in males, usually in the seventh decade of life. Histologically, these tumors reveal intracellular keratinization, intercellular bridges, and keratin pearl formation. However, they do not produce mucus.

There is a high incidence of regional and distant metastases. The prognosis for squamous cell carcinoma of the salivary gland is poor. Therapy consists of complete surgical resection and postoperative radiation therapy.

## **Patient presentation**

Malignant salivary gland neoplasms represent 3-4% of malignant head and neck disorders. The incidence is of 1-2 per 100,000 individuals. Neoplasms arising in the minor salivary glands have a poorer prognosis than those primary in the parotids. On average 20-25% of parotid gland tumors are malignant and the average age of presentation is 56.6 years. Parotid masses are usually identified by the patient themselves or loved ones, and patients present to surgeons usually complaining of an incidental mass. When assessing a patient with a parotid mass, it is helpful to ask if there is any pain associated with the mass, presence of lymphadenopathy, facial nerve function as well as lingual and hypoglossal functions. It is also helpful to assess trismus and fixation of the mass.

Less than 10% of malignant salivary disorders are metastases from other sites. Most of them are lymphatic metastases from skin cancer of face, ear, and scalp. The most common found are SCC and Melanoma. Elective superficial parotidectomy and neck dissection should be performed for primary melanoma of intermediate depth (1.5-4mm) located within periparotid drainage area.

### ***TNM Staging:***

- Susan McCammon, MDT1 Tumor less than 2cm
- T2 Tumor between 2cm and 4cm
- T3 Tumor greater than 4cm and/or extraparenchymal extension
- T4a Moderately advanced disease, invades skin, mandible, ear or facial n.
- T4b Very advanced disease, invades skull base, pterygoids or encases carotid

## **Areas of Controversy**

### ***FNA***

Fine needle aspiration (FNA) is a procedure by which cells are removed by aspiration with a small needle. The cytopathologist is unable to visualize structure of tissue and must make a diagnosis by cellular morphology. George Papanicolaou (1883–1962) is generally credited with the rediscovery of cytopathologic examination, which has been instrumental in decreasing cervical cancers. FNA relies on the ability to extract diagnostic information from the appearance of individual cells and cell clusters.

In order to be diagnostically helpful FNA should reliably distinguish benign from malignant, identify lymphoma and also identify metastasis from a cutaneous malignancy. Opponents argue that the results of an FNA don't change the management which is usually surgical except in lymphomas. They also argue that the FNA may obscure final diagnosis and that the frequency of inadequate sampling requires multiple biopsies, prolongs course and also increases cost. Proponent's argument is that FNA is important to distinguish benign vs. malignant nature of neoplasm, it is valuable in preoperative patient counseling and surgical planning. In addition they argue that FNA helps differentiate between neoplastic and non-neoplastic processes.

Among H&N sites, the parotid gland has the highest FNA inaccuracy rates secondary to:

- Sheer number of number and diversity of salivary gland tumors.
- Relatively uncommon – cytopathologist experience limited.
- Distinct tumor types often share some overlapping morphologic features.
- Some parotid carcinomas appear very bland and nonthreatening at cellular level.

Balakrishnan concluded that Fine needle aspiration cytology does not reliably distinguish a benign from a malignant primary salivary gland in the participating institutions. Where clinical teams use FNAC in an attempt to resolve this clinical problem, the results should be interpreted with caution and an ongoing audit of performance is required. In their study 46% of aspirates were suggestive of the final diagnosis, 31% were non-diagnostic, 15% were sampling errors and in 10% of cases the results were misleading. The sensitivity in FNA in detecting malignant disease was 79% with a sensitivity of 84% and positive predictive value of 68%. In addition they commented that FNA did not reliably predict/dx lymphoma, but may have avoided radical parotidectomy.

Heller et. al. concluded that complications of FNAB appear to be rare. They failed to identify any signs of tumor implantation by FNA. FNA resulted in a change in the clinical approach to 35% of the patients. They were able to avoid surgery in 27% of patients and performed a lesser procedure in 8% of patients as a result of FNA.

### ***PET Scan***

PET scan is becoming more useful in staging and follow-up of malignancies in general and can be helpful to rule out distant and regional metastases. In 69% of cases it can reliably predict the nature of the neoplasms. It has additionally demonstrated a nearly 100% sensitivity for malignancy but a false-positive rate of 30%. Its role therefore is not well defined yet. Complicating issues are the fact that PET scans are positive with inflammatory lesions such as Warthin's and in pleomorphic adenomas. Ozawa et. al. performed an investigation to determine the usefulness of PET in differentiating benign versus malignant parotid masses. They determined the accuracy was 53%, False-positive rate was 55% when the cut-off value for SUV was set at 3.5. This compared to Keyes et al., who reported an accuracy of 69% and false-positive rate of 30% for differentiation of benign and malignant masses using PET. PET identified all 26 lesions in the parotid of which 12 were malignant lesions. It correctly identified them all as malignant. However correct categorization in only 69% of cases because it incorrectly identified other benign lesions as malignant. Thus, it was not as good as the more conventional diagnostic methods, their correct categorizations being 85% (clinical), 87% (CT/MRI), and 78% (FNAB) in the same patients.

### ***CT vs MRI.***

MRI and CT scans both have virtues and downfalls. Ideally one would only need to obtain one scan and it would be relatively easy to obtain with minimal cost. In reality oftentimes in complicated cases the physician is forced to obtain both. Several authors have attempted to identify which study is best to distinguish several important features, such as nerve involvement, bone invasion, lymphatic spread and determination of which lobe of the parotid is involved.

CT is unique in that it provides excellent detail of tumor volume, is useful in evaluating the parapharyngeal space and can help with surgical planning in identifying the relation to

vessels and bony landmarks as well as identify involved lymphatics. It does however require contrast and radiation, and there can be artifact from dental fillings around the parotid. In contrast MRI does not require iodination or radiation, provides excellent soft tissue detail. MRI is superior in defining the tumor boundaries and is thought to be more useful to determine if nerve involvement present.

Koyuncu et. al. performed a retrospective review comparing CT and MRI in the detection of malignancy. They concluded MRI better at distinguishing intrinsic vs extrinsic. The inaccuracy rate of both MRI and CT was the same regarding the tumor infiltration. However MRI was threefold more expensive than CT scan. In the end they concluded that CT and MRI are morphologically equivalent studies and have the same diagnostic potential in parotid tumors. They additionally said MRI was better at determining perineural spread than CT. They listed several criteria to be used to determine nerve invasion on MRI: replacement of nerve with tumor, enhancement with gadolinium, and an increase in size of nerve.

Parker et. al. performed a more extensive investigation detailing the radiological findings in perineural spread of parotid neoplasms. They concluded that MRI was better in determining cisternal segment and cavernous sinus CT and MR imaging were virtually identical in demonstrating perineural tumor below the skull base. They also concluded that T1 weighed MRI before and after GAD is the study of choice if perineural spread is suspected. Fat suppression was identified to be beneficial around skull base. Generally, MRI indicated when nerve involvement suspected.

### **Post-Operative Radiotherapy**

Surgery is the primary treatment for patients with malignant tumors of the parotid gland, but a role for postoperative radiation in patients felt to be at high risk for recurrence is widely accepted. Two radiation techniques are commonly used for treating the parotid bed; one uses a pair of <sup>60</sup>Co or high-energy photon beams oriented at oblique angles to encompass the parotid bed (wedged pair), and the other uses an ipsilateral field treated peribeyond the range of the electrons. Garden et. al. reported updates on their experience using postoperative radiotherapy for selected patients with parotid malignancies, highlighting local and regional control, prognostic variables that may suggest a modification of treatment, and late complications of the two treatment techniques. They concluded that when radiotherapy is used there were a 9% local recurrence and 90% control rates at 10years. Additionally the need to sacrifice the facial nerve and perform a neck dissection was associated with local failure. Based off of their results they recommended postop XRT for:

- High-grade histology
- Recurrent disease
- Inadequate surgical margins
- Perineural invasion
- Extension of disease beyond the gland
- Nodal disease

## Facial nerve and elective neck dissection

The traditional surgical philosophy for parotid tumors has been to maintain continuity of the facial nerve, whenever possible, if the nerve is functionally intact preoperatively. If necessary, dissecting a branch of the facial nerve off the tumor without a true margin of normal tissue has been supported. This approach may facilitate uniform treatment of parotid tumors with minimal preoperative evaluation. However, increased use of fine needle aspiration allows diagnosis of adenoid cystic carcinoma preoperatively in 77% to 90% of cases and this information may be useful in preoperative counseling and surgical planning. Isel et. al. concluded that selective facial nerve sacrifice was associated with trends toward improved local control and survival but worse quality of life. Patients managed with postoperative radiotherapy had better local control rates than those without. N0 patients rarely developed metastases to regional lymph nodes.

Valstar et. al. performed a metanalysis to determine the utility of an elective neck dissection in the clinically negative neck. They reviewed a total of 39 publications from 1997 to 2007. They identified 83% (out of 871 patients) were staged N0 by palpation and radiology. In 23% of ELND pathologic nodes were identified. Elective treatment by either (selective) neck dissection or radiotherapy is, therefore, widely practiced. Regional recurrences are only 5% after aggressive therapy. There are several factors that are predictive of aggressive disease, if these are present a neck dissection should be performed as an adjunct to treatment to the primary site:

- High tumor grade
- Facial paralysis
- Older age (>54y/o)
- Perilymphatic invasion
- Extraparotid extension
- T3 or T4 disease

## Conclusions

Parotid carcinoma accounts for 3-4% of H&N cancers. Performing an FNA is an important aspect of counseling patients with parotid neoplasms even if the information revealed by performing it might be limited and should be analyzed with several other factors. FNA is especially important when facial nerve is involved.

There are several morphologies we will make a cytological diagnosis challenging especially in centers with low volume. CT scans are generally useful and MRI tends to be more useful when perineural spread is suspected

PET scans may play a role but not in the initial diagnosis. False positives seen in inflammatory process limits its usefulness in distinguishing benign from malignant. PET scan cannot reliably distinguish benign from malignant process. Post-Operative XRT indicated when facial nerve is involved or in clinically positive neck. Elective neck dissection maybe indicated in certain circumstances, such as those in which there is aggressive disease.

## Discussant's Remarks 2011-02-25 Parotid Neoplasms - Dr. Susan McCammon

Dr. Pernas, I thought that was an excellent talk. I think your introduction raised one of the more pertinent points about it which is parotid masses are a territorial practice which is shared between community practitioners and university practitioners and not inappropriately. I think it is entirely reasonable for community practitioners to do parotidectomies. That being said I think that there are times that they will find pathologies that they were not expecting and you will have a dividing line between people who are prepared to do a parotidectomy and people who are prepared to do a parotidectomy and neck dissection. It behooves us to be conscious of their self-consciousness about it and be willing to help whether postoperatively or in the initial workup.

I disagree with Dr. Quinn about the utility of fine needle aspiration biopsy mainly because if I'm going to do a neck dissection I'm going to like to know when I'm planning my operative day. This involves a time-difference with me, especially when working with residents in doing a parotidectomy with or with a neck dissection.

That being said, I would never use a fine needle aspiration result to talk me out of doing a parotidectomy. It basically only upgrades the treatment I plan to do, so I'm going to say that if you need a parotidectomy, a fine needle biopsy may give us more information, particularly if there's any suspicion that it might be a lymphoma. Squamous cell carcinoma, melanoma, those also are capable of changing the treatment you might select.

The only time I really accept a negative fine needle aspiration biopsy is when we're just going to watch it, or in people who are super-sick and in which we want to avoid surgery and sometimes in the older Wharthin's patients, because I think that the sensitivity and specificity for Wharthin's are pretty good. They tend to be bilateral and people do just fine with them.

Regarding PET scanning, the place where we see that the most is among our colleagues in the community who have the PET scan and like to use it and find a lot of incidentalomas because because Wharthin's and some of the other tumors are not just positive on PET. They're like "super-positive" and SUV's are thirty and so you will get a lot of referrals for that and it's just a matter of education.

Treatment of the facial nerve: I remember when I was in training it was always a great big deal of whether you were going to sacrifice it or dissect the tumor off of it, if you're going to reconstruct at the time or delay reconstruction. I think typically now reconstructing at the time of surgery is preferred with contralateral, greater auricular, or the sural nerve, with some controversy over whether to use the ipsilateral greater auricular nerve for oncologic reasons.

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