INTRODUCTION

When a patient presents to clinic with a neck mass, there is a wide array of disease processes in the differential diagnosis that this mass could represent. Much of the clinical diagnostic decision making can be guided by specific patient factors such as age, sex or previous exposures. Though not always, a congenital neck lesion such as a thyroglossal duct or branchial cleft cyst typically presents in the early part of life. In contrast, an older adult with a new neck mass in the context of a heavy smoking and drinking history would be most concerning for metastasis from cancer, most commonly squamous cell carcinoma of the upper aerodigestive tract. A ring-enhancing neck mass on contrasted-CT scan would point towards an abscess as the diagnosis, and a lateral slowly enlarging neck mass with audible bruit on auscultation would suggest a vascular lesion such as paraganglioma.

PARAGANGLIOMAS IN GENERAL

The term “paraganglioma” is a generalized term for a neuroendocrine neoplasm found in the autonomic nervous system. Though the majority of paragangliomas are derived from the sympathetic nervous system in the form of a pheochromocytoma, the bulk of the paragangliomas of the head and neck originate from the parasympathetic nervous system. These tumors are comprised of neural crest cells that primarily function as bloodstream chemoreceptors. The most common locations for paragangliomas of the head and neck are within the carotid body and the middle ear, or associated with the vagus nerve and internal jugular vein. They have also been more rarely found in other locations above the clavicles including the nose, orbit, thyroid, and larynx (only a few incidences reported in the literature).
EPIDEMIOLOGY OF PARAGANGLIOMAS

The vast majority of paragangliomas tumors in patients are pheochromocytomas located adjacent to the adrenal gland, representing 90% of all paragangliomas. The next most common are abdominal paragangliomas (8.5%) and only approximately 0.3% of all paragangliomas are located in the head and neck. Overall, they tend to occur in middle age adults and are more common in females.

When speaking in regards to paragangliomas specifically localized to the head and neck, carotid body tumors by far are the most common making up 60% of them. Jugulotympanic tumors are second most common, and the least common of these would be the glomus vagale comprising only 5%. Luckily, the majority of these are benign, although malignancy can be found in approximately 6-16% of carotid body tumors and 4% of jugulotympanic tumors. As noted earlier, much more rare areas for these to be found include the larynx, nasal cavity, and orbit.

GENETICS OF PARAGANGLIOMAS

Somewhere between 5-10% of paragangliomas are thought to arise from a familial gene mutation with an autosomal dominant inheritance pattern. Researchers have isolated a group of defective genes known as PGL 1, 2, and 3 (also termed the SDH gene). This gene is found at the 11q23 locus, and one may test for this gene defect when suspecting a familial origin to a paraganglioma.

In general, when a paraganglioma has familial inheritance, one should strongly suspect and investigate for multiple tumors located elsewhere in the body. Multiplicity of tumors occurs in 78-87% of familial cases. Familial tumors also tend to be bilateral and occur at an earlier age of onset. They may also be found occurring in patients with more well-known genetic syndromes such as MEN Type IIA and B. In order to aid in the detection of multiple tumors, one can implore the indium pentetreotide test which specifically labels somatostatin receptors often present in these tumors.

TYPE OF HEAD AND NECK PARAGANGLIOMAS AND APPEARANCE (INCLUDING HISTOLOGY)

Below listed are the four main types of paragangliomas in the head and neck:

1. Carotid body
2. Glomus jugulare
3. Glomus tympanicum
4. Glomus vagale

It is important to note that the tumors glomus jugulare and tympanicum can be lumped into the single category of “jugulotympanic tumor”, and the most recent classification system refers to them as part of the same disease process but in different locations. Older texts and articles will primarily refer to them by the former terms with “glomus” in their name but new literature primarily uses the latter term in order to avoid confusion with glomus tumors originating in the integumentary system.
The gross appearance of these tumors is similar to one another despite their location in body given that paragangliomas are all highly vascular lesions. This gives them a definite reddish appearance and makes them apt to easily bleed during surgical resection. Grossly, they are firm and rubbery in nature. Otoscopic view of a glomus tympanicum tumor will demonstrate a deep red mass medial to the tympanic membrane. Pathologists typically describe the carotid body tumor as having a deep red to brown/gray color in gross appearance.

**HISTOLOGY OF PARAGANGLIOMAS**

The histological features of these tumors certainly serve to aid in their diagnosis, and these features have little variability, attributing to a classic appearance to these lesions under the microscope. The tumors are primarily composed of two main cell types: the central chief cells (Type I) and the enveloping sustenacular cells (Type II cells).

The Type I chief cells form the primary cell type within the tumor. These cells appear light pink with a prominent nucleus on H and E staining. Chiefs cells stain positive for chromogranin most importantly but also synaptophysin, neuron-specific enolase, serotonin, and neurofilament stains. If the paraganglioma is a catecholamine-secreting tumor (rare in the head and neck) causing systemic symptoms like hypertension and anxiety, it is the type I cells that contain the catecholamine-bound granules leading to this. Type II sustenacular cells are the fibrovascular support cells that encircle the Type I cells. These sustenacular cells stain positive on S100 staining whereas the type I cells stain negatively for this chemical. The combination of these two cells forms a structure that appears as a nest of cells, historically termed “Zellballen” seen on lower powered microscopy.

**GENERAL WORKUP/TESTING FOR PARAGANGLIOMAS**

Lab testing for paragangliomas of the head and neck has some utility though there is not a large place this. It is important to note that while abdominal paragangliomas often times secrete catecholamines, corresponding tumors in the head and neck are typically non-secreting and thus non-functional. Only 2-4% of these patients present with catecholamine-driven symptoms such as hypertension and tachycardia. Routine screening for a functional tumor in the form of urinary catecholamine testing is usually only indicated when the tumor is suspected to be familial in origin as these have a higher likelihood to be functional.

Radiography of these tumors, on the other hand, is the preferred diagnostic modality. Often times a combination of multiple imaging modalities including ultrasound, CT, and MRI is used for proper diagnosis. Angiography is the gold standard for diagnosis and often aids in treatment planning and initiation of therapy (e.g. pre-operative embolization). Though needle or open biopsy of these lesions is not completely contraindicated, it is often not necessary and causes unnecessary risk of bleeding and morbidity for the patient.

**TREATMENT CONSIDERATIONS FOR HEAD AND NECK PARAGANGLIOMAS**

Preoperative embolization of these tumors is fairly common practice to attempt to reduce the size and vascularity of the lesion. This ultimately aids in decreasing intra-operative bleeding during
resection. There is some controversy about the overall utility of performing this procedure as its opponents argue that it makes no measurable or statistical difference in outcomes and carries (as any angiogram would) increased risk of stroke. If the surgeon opts to proceed with this as part of the treatment plan, it is preferred for the patient to undergo surgical resection of the tumor within 2 days before blood vessel regrowth can occur.

Though surgery is the mainstay of treatment, there is a considerable role for radiation therapy as an adjunct or primary treatment of head and neck paragangliomas. There is a substantial amount of evidence to support radiation as primary treatment over surgery given the substantial amount of morbidity seen commonly after surgery.

Much of the decision to use radiation revolves around tumor characteristics and individual patient factors. For example, elderly patients often sustain significant morbidity and mortality from surgery so radiation is often the best treatment for them. In addition, location of the tumor in relation to major nerves, arteries, or veins may drive the decision for radiotherapy over surgery.

There is substantial literature to advocate for radiation at least as an adjunct to surgery if not as a substitute. Hinerman et al. (2008) claimed that “fractionated radiation therapy offers high probability of tumor control with minimal risk to patients.” This study of 121 head and neck paragangliomas undergoing radiotherapy demonstrated tumor control rates of 96%. They considered “control” or “cure” to be equated with absence of tumor progression, and this was measured with a mean follow up time of 10.6 years. Similarly, Sheehan et al. (2010) demonstrated significant control of glomus jugulare tumors utilizing gamma-knife radiosurgery. Surgical resection will be discussed later as it pertains to specific tumor types.

**MALIGNANCY OF HEAD AND NECK PARAGANGLIOMAS**

Somewhere between 4-15% of head and neck paragangliomas are considered to be malignant. The most malignant subtype is the vagal tumor with a malignancy rate of 16-19%. It has long been the opinion of pathologists that malignancy of these tumors can only be concluded when there is lymph node or distant organ metastasis found in a patient. Even as recent as 2012 Offergeld reasserted this to still be the case, stating that “tumor invasion to adjacent structures such as bone does not indicate biologic malignancy.”

To further elucidate this phenomenon, Chapman et al. (2010) studied the clinical, histological and radiologic features of these tumors in a total of 84 patients (77 benign and 7 malignant). Of the 7 considered malignant, 6 of them were deemed this based on distant metastasis. The remaining malignant tumor was labeled this due to possessing several very locally-aggressive features. This particular non-metastatic malignant tumor demonstrated vascular, capsular, lymphatic, and perineural invasion. The same study also looked at clinical factors in the individuals with malignant tumors, and they found patients with significant pain on presentation, those who presented with enlarging cervical mass in the last 12 months, or those with younger age of presentation all were more likely to malignant.
CAROTID BODY TUMORS: ANATOMY, PHYSIOLOGY, AND SIGNS/SYMPTOMS

The carotid body is a chemoreceptor organ made of glomus cells that has the primary function of sensing the chemical make-up of the blood, specifically sampling levels of pH, oxygen, and carbon dioxide. The primary stimulators of the carotid body include academia, hypercarbia, and hypoxia. These stimulators result in downstream sympathetic nervous system effects, in turn causing increased heart rate, blood pressure, respiratory rate, and pulmonary tidal volumes. Low partial pressures of oxygen are thought to be the most potent stimulant of the carotid body.

Grossly, the carotid body is a small reddish brown-tan ovoid structure only 3-5 mm in diameter. It is located within the adventitia of the common carotid posterior and medially to the carotid bifurcation. Blood supply comes primarily from small feeder blood vessels from the ascending pharyngeal artery, a branch of the external carotid artery. Afferent innervation leaves via Herring’s nerve which is a branch of the glossopharyngeal nerve. In regards to the pharyngeal space, carotid body tumors are considered to be the most common tumor of the post-styloid pharyngeal space.

Carotid body tumors generally present as a painless swelling in the lateral neck. This is mainly found anterior to the sternocleidomastoid muscle at approximately the level of the hyoid bone. They are fairly slow growing, with an average doubling time of about 7 years. Auscultation of the mass may reveal an audible bruit. A classic sign of a tumor of the carotid body (known as Fontaine’s sign) is seen when the tumor is palpated and it is laterally mobile but is fixed in the cranial-caudal direction.

Fortunately only a small number of them (10%) present with cranial symptoms. Given its coinciding location within the carotid sheath, the vagus nerve (X) is the most common cranial nerve affected, yet palsies may be routinely seen in cranial nerves IX, X, XI, and XII as well as the sympathetic chain depending on the size and erosive qualities of the mass. Involvement of these nerves can result in many deficits including hoarseness, dysphagia, shoulder/neck weakness, and tongue weakness.

RADIOLOGY OF CAROTID BODY TUMORS

As mentioned previously, multiple modalities are used during diagnosis and treatment of paragangliomas of the head and neck. Carotid body tumors especially present with very classic radiological findings. Though not the most specific testing, ultrasound represents some of the least invasive and basic radiographic testing available. As is true on multiple imaging modalities, these tumors can be seen splaying the external and internal branches of the carotid artery (known as Lyre’s sign).

CT scan gives considerable amount more detail which will show as a relatively hyper-dense mass. Given that these are hyper-vascular tumors, unless it is contraindicated for renal disease purposes CT scanning should be performed with IV contrast in order identify the tumor’s relationship to major blood vessels. On MRI scan these tumors will display as iso-intense to muscle on T1 imaging and hyper-intense on T2 imaging. Particularly they have avid enhancement on post-contrast images. Some radiologist describe these tumors as having a “salt and pepper” appearance on MRI based on varying areas of black signal flow voids (pepper) and high signal foci (salt).
When definitive diagnosis is warranted, angiography is the best modality. High quality CT and MRI have made this modality more obsolete. There is significant role for angiography in treatment as means for preoperative tumor feeder blood vessel visualization and embolization. In addition, angiography is the best means to demonstrate the classic “Lyre’s” sign which is the splaying of the internal and external carotid arteries as described above.

SURGICAL CONSIDERATIONS AND TECHNIQUE FOR CAROTID BODY TUMORS

There are few major tenants to keep in mind for surgical resection of carotid body tumors. First, the surgeon must be mindful of all cranial nerves in the surgical field. The most readily involved are again IX, X, XI, and XII and given its frequent location on the posterior edge of these tumors, the superior laryngeal nerve (branch of X) is the most common nerve injured during this surgical procedure.

In general, there is a significantly higher risk of nerve and arterial injury with increased size of tumor at time of resection. In these cases it is not uncommon to avoid anesthesia paralytic agents so that stimulation of these nerves can be detected. When bilateral carotid body tumors are present, it is recommended to only remove one at a time. This lessens the chance of hemodynamic instability potentially caused by bilateral disruption of the carotid sinuses in addition to possible bilateral vagus nerve injury.

Below listed are the steps of the procedure as recommend by Meyer’s Operative Otolaryngology:

1. Incision→ place transversely hidden in skin crease
   -Alternatively vertical incision over SCM (carotid endarterectomy type)
2. Dissect through subcutaneous tissue with skin flaps elevated down to SCM
3. Find the sternocleidomastoid muscle, retract posteriorly to expose the carotid sheath
4. Dissect IJV off the carotid artery
5. Identify and dissect out CN X and CN XII and place vessel loops around them
6. Identify the common carotid; skeletonize it and place vessel loop around it
7. Start sub-adventitial dissection on the CC, directed superiorly up to bifurcation
   -This begins just superior to commonly seen venous plexus overlying CC
8. Carry subdental dissection superiorly onto External Carotid
   -Recommend clamping, cutting and suture-ligating ECA to aid in deeper dissection,
   especially for larger tumors extending to prevertebral fascia
9. Dissect tumor off the Internal Carotid, remove, and then close

The venous plexus mentioned in step 7 can consistently be found approximately half the distance between the clavicle and carotid bifurcation. Also the sub-adventitial dissection is necessary because a normal carotid body lies within this plane in the bifurcation so the tumor will as well.

SHAMBLIN CLASSIFICATION AND SURGICAL COMPLICATIONS

The Shamblin classification system was initially developed based upon intra-operative findings in order to help predict post-operative morbidity in these highly vascular carotid body tumors. Shamblin
class Type I is the least invasive tumor type which correlates to splaying the main carotid branches but not encasing them. These tumors are minimally attached to blood vessels and are removed by complete resection with minimal risk to the patient.

Type II Shamblin class are more adherent to the vessels and partially encasing the external and internal carotids. Resection of these lesions carries higher risk of complication but is still possible. The most invasive lesions are Type III Shamblin which indicates the external and internal carotids are completely encased by the tumor. Often times these tumors are considered unresectable. If resection is undertaken, it is highly risky and often requires interruption of blood flow to the brain with vascular reconstruction.

Given the vascularity of carotid body tumors, bleeding from the carotid artery and/or jugular vein is a common and expected complication of surgery though usually manageable with proper technique. Cranial nerve injury is also common. Injury of CN X including the superior laryngeal branch leads to aspiration and vocal issues. Loss of CN XI can cause shoulder pain and weakness, and CN XII injury causes speech and swallowing issues for the patient. It is important to note that there is a significantly high rate of aspiration and dysphagia with patient’s with concurrent CN X and XII injuries. Disruption of the adjacent sympathetic cervical chain which lies posterior to the carotid sheath may lead to an ipsilateral Horner’s syndrome (ptosis, miosis, and anhydrosis), and blood flow interruption to the carotid arteries or associated embolism may both cause stroke.

**JUGULOTYMPANIC TUMORS**

It has only been recent that glomus tympanicum and glomus jugulare tumors have become grouped into the same category. Glomus tympanicum tumors are specifically confined to the middle ear space. Similar to jugulare tumors, they arise from the paraganglia tissue on the tympanic branch of CN IX (Jacobson’s nerve). On the Fisch Classification scale of jugulotympanic tumors, this is a Fisch Type A, and it is the most common tumor of the middle ear. 80% of patients present with pulsatile tinnitus and 60% have ipsilateral hearing loss. On CT temporal bone scan, classically seen is a round mass adjacent to the cochlear promontory.

Glomus jugulare tumors arise from the paraganglia tissue around the jugular bulb and may either arise along Jacobson’s nerve (CN IX; same as glomus tympanicum) or Arnold’s nerve (CN X). Again the most common presenting symptoms are pulsatile tinnitus and hearing loss. For imaging, CT can be used to try to delineate these from glomus tympanicum, and MRI may utilized to define the extent of the disease. When compared to carotid body tumors, glomus jugulare tumors have a much higher incidence of cranial nerve injury at 30% and also have a tendency toward tumor multiplicity (50% in familial cases).

The Fisch Classification system A-D is the primary system used to categorize these tumors. The most basic is Type A which designates glomus tympanicum tumors since they are limited to the middle ear cleft. Type B tumors are limited to the tympanomastoid area. Tumors involving the infralabyrinthine compartment of the temporal bone are considered type C and subdivided into C1-3 based on their degree of extension into the petrous apex and subsequent portions of the carotid canal.
Lastly, Type D tumors represent intracranial extension with Type D1 having less than 2cm intracranial extension and D2 with greater than 2cm.

The most basic tumors such as Type A require less invasive surgical approaches such as tympanotomy, and the more extensive tumors have need for corresponding approaches such as transmastoid and infratemporal fossa. When one carefully analyzes the skull base and the location of the foramina that these nerves exit, one can understand how multiple cranial nerve deficits may be present in patients with these tumors given just how closely these structures are juxtaposed normally.

**GLOMUS VAGALE**

The last and possibly most ominous paraganglioma of the head and neck is the glomus vagale tumor. These tumors arise from one of the three ganglia situated along the vagus nerve as it approaches and enters the skull base. There is an inferior (a.k.a nodose ganglion), middle, and superior ganglion. These tumors are the most likely of the head and neck paragangliomas to become malignant. Luckily they are the rarest, representing only approximately 5% of the head and neck paragangliomas.

Grossly these tumors are situated more superior than carotid body tumors would be and can also be distinguished by the fact that they reside between the internal carotid and internal jugular vein instead of between the carotid branches as their corresponding tumor does.

Several factors contribute to the malignant status of these tumors. For instance, 22% of vagal tumors already have intracranial extension at the time of diagnosis, and this is the primary cause of death in these patients. Also, up to 50% exhibit cranial nerve deficits at time of presentation, primarily affecting CN X (hoarseness, aspiration) as well as IX, XI, and XII.

The staging system for glomus vagale tumors was developed in 1993 by Dale et al. and is fairly simplistic. Type I tumors lie in the parapharyngeal space without evidence of jugular foramen invasion. Type II tumors have jugular foramen invasion but do not violate the skull base, and Type III tumors present with deep invasion of the jugular foramen and/or middle ear with extension into the skull base. This gives the Type III tumor a classic “dumbbell” appearance.

Primary radiation is often considered a viable treatment option given their tendency towards invasion at time of presentation, but if and when surgical resection is attempted, it often requires performing a high lateral cervical incision with possible mandibulotomy for proper exposure. It is certainly prudent to involve the neurosurgical team in cases of intracranial extension. Routinely the involved vagus nerve must be sacrificed creating expected dysphagia and aspiration complications though these symptoms are often present preoperatively as well. Patients expected to have unilateral vocal paralysis due to vagus nerve sacrifice may require scheduled thyroplasty vocal medialization at time of surgical resection to attempt to prevent post-operative aspiration. Again the concomitant CN X and XII injury commonly seen during this type of tumor resection has been shown to create the highest risk for aspiration post-operatively.
SUMMARY OF PARAGANGLIOMAS OF THE HEAD AND NECK

In comparison to other masses of the head and neck such as squamous cell carcinoma, head and neck paragangliomas are relatively rare. Despite this, they are significant and interesting enough to warrant knowledge of these lesions. In general paragangliomas of the head and neck are slow growing and typically benign. The carotid body is the most common of these, followed by the jugulotympanic tumors, and the vagale glomus tumors as least common. Fortunately, there is an inverse relationship between commonality of the tumors and their malignancy, with the vagale tumor having the highest propensity for malignancy. Though there has been an increasing role for radiation as adjuvant (and even primary) therapy, surgical resection is the mainstay of treatment, and radiation is usually reserved for the most advanced lesions and for people that cannot tolerate undergoing anesthesia.

FACULTY DISCUSSION:

DR. SUSAN MCCAMMON:

Thank you, Dr. Yantis. That was a terrific talk, a great summary of paragangliomata. Dr. Resto has asked me to comment on my experience and training at Memorial Sloan-Kettering where typically we did not embolize these with the thought that there was a transient inflammatory response that would make it more difficult to resect them. I think the incidence and morbidity of the cranial neuropathies that can result after surgery are really significant, and most of the people that I worked with are tending more toward radiating these now.

The larger ones are more invasive ones really only in early stage carotid body tumor - a one or two cm. one I would really resect. But it depends a lot on the patient’s age, functional status, but to take a young person and to give them a high vagus injury, especially if there’s a risk of twelfth nerve injury, as well virtually guarantees almost chronic and almost insurmountable aspiration, not just because of the cord paralysis, but also because of the loss of sensation plus the loss of tongue mobility. So that’s the thing I would add: the loss of sensation along with the loss of mobility really exacerbates the cord paralysis. Now I’ll turn it over to Dr. Resto, your Mentor.

DR. VICENTE RESTO:

Thank you, Dr. McCammon. Dr. Yantis, that was a great talk. So I guess over all, at a high level, I would echo what Dr. McCammon just said. I think that the experience with the often serious deficits that result from surgical intervention really has driven folks to observe these. Many times one can follow them with imaging, and if there is a tumor that is producing minimal symptoms, which is often the case, often they are found incidentally. You can follow them prospectively and show that there is little or no growth, observation is really at the top of the list. Traditionally resection was rooted in the fact that there has been this reported low rate of malignant transformation, but the reality is that the rate is so low that when put in context with the adverse effects of resection really have made over the history, now a strong argument for observation and or radiation - specifically if there is an elderly
patient. With a growing tumor, radiation can be useful in arresting growth. It does not necessarily get rid of the tumor.

Two points: if you choose engage in surgery of these tumors, one is to recognize that you will have significant cranial nerve defects particularly in the vagal version of these paragangliomas. I just don’t know a whole lot of people who will go up there and not have at least transient and very often permanent cranial nerve injury. The other is that the surgically approach is really all about management of vascular structures. That’s where certain maneuvers such as early take of the external carotid at its root when handling a carotid body tumor is a common technique that comes in very useful. Recognition that the ascending pharyngeal branch will not uncommonly come out of the bifurcation itself. So, one of the more common injuries is when you’re trying to dissect out the carotid body tumor from the base of the bifurcation is to end up with a rather sizeable rent in that area. Having vascular surgery, or some expertise in patching or repairing the carotid at that site, it might be mandatory when handling some of these tumors.

When talking about the vagal tumors again, it’s not rare at all that they engage the jugular foramen, and at that the jugular vein tends to be collapsed, and then it’s not uncommon to have injury of the internal jugular at a very high location which makes it technically challenging to repair. These are all things that need to be thought of ahead of time and having a definitive plan of how to manage them. These have always been a very tantalizing set of lesions.

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