Dr. Jason Barnes:

Hey there, welcome to another episode of ENT in a Nutshell. My name is Jason Barnes. And today, we are discussing esthesioneuroblastoma, and we are joined by fellowship-trained rhinologist, Dr. Garret Choby, and fellowship-trained skull-based neurosurgeon, Dr. Jamie Van Gompel. Dr. Choby, Dr. Van Gompel, thanks so much for being here.

Dr. Garret Choby:

Thanks for having us.

Dr. Jamie Van Gompel:

Thank you.

Dr. Jason Barnes:

We'll start with presentation. Not everyone presents with quote unquote "esthesioneuroblastoma", so when you see a patient who might have this process, what are some of the typical findings that you see, when you first evaluate patients?

Dr. Garret Choby:

Thankfully in our clinic, most do present with esthesioneuroblastoma, but it's not certainly across the board. In a number of meta-analysis that have been done, the most common symptom, that presents is with nasal obstruction. Other things can be diminished sense of smell, so hyposmia or anosmia; epistaxis is occasionally common, and other things can occur as well; headache, vision change, et cetera, are occasional presenting symptoms. The last thing I'll mention, that once in a blue moon, someone has a neck node, and gets an FNA biopsy and it comes back as an esthesio. It's an uncommon way to present, but every once in a while, someone does present with a neck node, as opposed to a nasal symptom.

Dr. Jason Barnes:

And before we fully get into workup, when you evaluate a patient in clinic, what might you find, more specifically, on endoscopic exam?

Dr. Garret Choby:

So, typically, all these pieces will certainly by in an endoscopic exam. These tumors most commonly arise in the olfactory cleft. So, they're a high nasal volt tumor, usually they're moderately vascular and kind of appear as a fleshy mass in the nose. Certainly a nasal endoscopy and likely a biopsy, assuming there's been some imaging done, is in order, as well as a thorough neck exam is important as well.

Dr. Jason Barnes:

And could you describe the classic patient who walks into your clinic with this?

Dr. Garret Choby:

There's no specific predisposing factors for this disease process. There's been reported a number of different age distributions, in some studies has been a bi-modal age distribution. So, a little bit younger and then older folks. When you look at the meta-analysis was done a few years back, most patients present in middle to late age. So forties, fifties, sixties are pretty typical presenting timeframes.

Dr. Jason Barnes:

And moving on from initial presentation, what is an esthesioneuroblastoma? What's the pathophysiology?

Dr. Jamie Van Gompel:

That cell type that most people believe cause this is called the bipolar cell from the nasal epithelium. So, it's usually in the upper 1.5 centimeters of the nasal vault. And although it's never been actually proven like it is in some other diseases, it is true though, that these do stay truly confined to that either paranasal space in the upper mid portion of the nose.

Dr. Garret Choby:

Yeah. When I think about this, to a certain extent, I think of it as this will probably get to be this small round blue cell tumor, or a neuroendocrine tumor. And as I was trained by, [inaudible 00:03:04] and this sticks to me forever, all credit goes to Dr. Steinman. These tumors, he describes as good, bad and ugly.

An esthesioneuroblastoma was sort of in that bad-ish range. Whereas it's cousins, that are also neuroendocrine tumors like SNEC, sinonasal neuroendocrine carcinoma, or SNUC, sinonasal undifferentiated carcinoma, are in that ugly range if you will. But it is in this sort of neuro epithelium differentiated cell type.

Dr. Jason Barnes:

Sure. And you started to talk about pathology and you've mentioned small round blue cell tumors. Are there any other buzz words related to this pathology type?

Dr. Garret Choby:

There are a few that you might see on certain examinations, if you will. Homer Wright Rosettes are present on some of these, about a third of patients. There's also one of, a bit less common, that you can see something called Flexner-Wintersteiner Rosettes, and that's a little bit less common than the Homer Wright Rosettes, but occasionally are seen on histopathological examination.

Dr. Jamie Van Gompel:

I'll add a little bit about, also, that historically what you see in papers about esthesioneuroblastomas, they have a very hard time differentiating between what were some of the tumors that Dr. Choby mentioned, like SNUCs, and actually the higher grade. And we'll get to that a little bit later esthesioneuroblastoma. It's a pathology in evolution, if you will, and not even institutions can actually agree that some of these are the same types of tumors.

So, in fact, when we look at the series that have come from Mayo versus the series that have come from the University of Virginia, we disagree on what a Hyam's Grade 4 lesion is for these. So, we're getting better and better with them. But what is also interesting now is, if we look at some specific molecular markers, like INI-1, which is becoming a hot topic, that some esthesioneuroblastoma express this and some don't. So I think, eventually, we'll probably get to a molecular diagnosis for this, but right now that's not currently where we're at.

Dr. Garret Choby:

Yeah. I agree, a hundred percent. It's a really evolving field. It's pretty interesting, actually.

Dr. Jason Barnes:

And what else do you put on the differential diagnosis when you see these patients?

Dr. Garret Choby:

We think about a lot of different things, certainly a number of semis and malignancies come to mind. Squamous cell carcinoma is a common one; I already mentioned both SNEC and SNUC, so sinonasal neuroendocrine or undifferentiated carcinoma. Other things are possible as well, rhabdomyosarcoma can occur. Lymphoma is one we see from time to time in that area. Another small round blue cell one is a Ewing sarcoma, which is a pretty unusual one, but one that will be entertained on the differential. Last one that I'll mention is also a sinonasal mucosal melanoma, another other small round blue cell tumor that can occur anywhere in the nasal cavity or paranasal sinuses.

Dr. Jamie Van Gompel:

Lymphoma is probably the most important one to differentiate it from because they can look very similar on imaging contrast, enhancing, eroding the skull base and has a completely different treatment algorithm than one would have with, with this type of tumor.

Dr. Jason Barnes:

And when we move on to work up, what is the next step in workup after physical exam and folks, you expect this tumor?

Dr. Jamie Van Gompel:

If they're in clinic with you and you have imaging, adequate imaging, the most important thing I think is biopsy.

Dr. Garret Choby:

Agreed.

Dr. Jason Barnes:

And what are the imaging studies that you would obtain if they didn't come with them? What would you be looking for?

Dr. Jamie Van Gompel:

It's an interesting discussion because it's different, again, across the country. Most of these patients walk in with a CT, they'll see some bony erosion of the skull base. It's nice to have an MRI because all the things that we were talking about earlier have different appearances on them. But this is typically a uniformly enhancing mass that is in the upper nasal vault. It can extend into the paranasal sinuses, which then makes it a Kadish B lesion if it erodes through the skull base and gets into the olfactory tracts nerves, and also into the brain.

Those are then considered Kadish C lesions, or extension into the orbit. But an MRI is important in understanding that because you don't necessarily see that, especially on a sinus CT. Patients that have advanced disease also sometimes we then get on and think about getting things like PET scans, especially for Kadish C lesions. But CT is probably the most important, and then the nasal endoscopy. And then if they're in clinic with you, and it's not something that you would think is a JNA, or something

like that, obviously you don't want to biopsy that in clinic. Biopsy is the most important next step, I think.

Dr. Garret Choby:

Yeah, I agree. Now, I'll just add there, in my opinion, intro clinic and in clinic biopsy is very important, and I'm pretty aggressive with those. If I don't think I'm going to cause a major hemorrhage or a CSF leak based on the imaging in the characteristic appearance, it really helps us to plan our surgical approach. And it makes sure we're not going to take a patient with a lymphoma to the operating room, with a planned six hour section that ends up being a frozen section lymphoma instead of an esthesio, and we're canceling a whole day of surgery.

Dr. Jason Barnes:

And quickly going back to MRI, I've seen stuff about this dumbbell appearance. Is that an accurate thing? Do we see that on MRI?

Dr. Jamie Van Gompel:

I don't think that that's that reliable. What that refers to is tumors that are going through the olfactory file and having something above the skull base, and something below. And these things can look a bunch of different ways. And in fact, it can be very difficult to interpret sometimes because they sometimes trap secretions behind them or in the frontal sinuses. And there's a lot of different things to look at. And I don't know that a dumbbell appearance is a very reliable characteristic for this.

Dr. Jason Barnes:

Sure. Now, Dr. Van Gompel, you started mentioning Kadish grading system. Do you mind quickly reviewing that with us?

Dr. Jamie Van Gompel:

There are a number of other grading systems, just so that the listeners are aware of, there's a UCLA based system that's based on TNM grading. But the most common system is the Kadish system which has been modified. So, the Kadish system comes to us from the MGH system based on a very limited number of patients, initially. And what they did is they broke down the tumors into A, B, and C. They didn't have D at that time.

That system said that Kadish A was confined to the nasal cavity. Kadish B was extension in the paranasal sinuses. And Kadish C was tumor beyond the nasal cavity and paranasal sinuses, which could include either involvement of the cribriform plate, the base of the skull. So, erosion on the CT through, into the intracranial cavity.

Or also, which could be separate, not necessarily seen with brain invasion, would be orbital invasion, as Kadish C. Now, Moriarty added, now almost a decade or more later, the D classification, which was, where patients had clearly presented with lesions in the cervical nodes or elsewhere. So, these could be true metastasis. Now, we don't consider cervical lymph nodes as being metastatic, we consider this regional disease. But distant metastases would involve with that, too.

Dr. Jason Barnes:

And we also start to talk about the Hyams grading system here. We probably don't need to go through all of the details since it's a somewhat detailed histologic chart. But can you talk to us a little bit about that, and how it helps you with management?

Dr. Jamie Van Gompel:

So, the Hyam system can be applied to many adenocarcinomas, and it's being applied in this neuroendocrine subset here. It gives us some things that tell us if tumors can look more aggressive under the microscope. And for a long time, people didn't really know if Hyam's grading system was more important than Kadish, and vice versa. But there are a number of independent studies, including studies from our institution, as well as MD Anderson, that demonstrate that Hyam's grading is an independent risk factor for these tumors being aggressive.

Most importantly, I don't think it's worth getting caught up into whether or not a tumor is a Hyams grade, one, two, or three or four, and memorizing the criteria that they have. But knowing that a Hyam's grade one or two is kind of a low grade, more low grade lesion, and Hyam's three and four is more of a high grade lesion, I think is very important. And those can be managed differently, depending on the institution.

Dr. Jason Barnes:

And one more question about workup, we mentioned metastatic disease. If you biopsy someone positive in clinic, do you always get a PET-CT to work up for metastatic disease?

Dr. Jamie Van Gompel:

So, probably not the best use of resources. Some people do recommend that, now. But smaller lesions, low Hyam's grade lesions, we wouldn't recommend that. Now, I would tell you that you have to push your pathologists even here, but I think most places, to give you the Hyam's grade lesion, or they give you the Hyam's grade scoring on your particular tumor. But PET scamming, we reserve for high Hyam's grade lesions, Kadish C and D lesions. Obviously, D lesions.

Dr. Garret Choby:

I'll also mentioned that it depends on what study you look at. Only 5% of patients will have a neck node at diagnosis. So, as far as resource utilization, unless they're a high grade or advanced disease, it may not always make the most sense to get a PET-CT. Now, I will say that most people, by the time they come, may have had a PET, or they've had at least a neck CT scan done, but I would echo those sentiments as well.

Dr. Jason Barnes:

So, we've talked about workup, we've talked about pathophysiology. So, say you confirm the diagnosis and the reason I appreciate both of you being in the room here is so that we can talk about treatment, too. What is your typical approach to managing these tumors?

Dr. Garret Choby:

I think that we'll probably discuss this one together because this is a pretty nuanced discussion we have amongst ourselves, pretty frequently. Again, presume there's no metastatic disease, we'll say in these cases. For localized tumors, we treat the majority of these now with an endoscopic and a nasal resection.

We'll talk a little about nuances of olfactory bulbar section or nod or bilateral unilateral. Now, there are some tumors that have a lot of intracranial extension or extension over the orbit, in which case other adjunctive open approaches are also needed. I would say, in our hands, majority nowadays we can treat with an endoscopic endonasal approach.

Dr. Jason Barnes:

And although we won't talk about the actual surgical steps, can you paint a picture for our listeners of what surgery looks like?

Dr. Jamie Van Gompel:

Let's back up just a little bit, though. Just to point out again, we've written a lot about how it's different across the country and across the world on this one. So, surgical approach, not everybody goes to surgery right away on these. In fact, UVA and I believe MD Anderson, and some other centers do upfront neoadjuvant therapy in all tumors. So, that sickness, it's an important discussion even here.

So, even in our hands, even though we favor going to surgery first, when we look at a series of over a hundred tumors here, we consider we only go to surgery if we think the tumor can get a margin negative resection. If we cannot achieve a margin negative resection, and that there's a little bit of, again, going back to the nuances about orbital, we do orbital preservation, regardless of margin negativity. We would then start with neoadjuvant therapy, here. And a lot of people would just start with neoadjuvant therapy.

They would go through typically, several cycles and then they would reimage. And at that point in time, go to surgery. Now here, like I said, if we can get a margin negative resection, that's what trumps everything, regardless of approach, whether we go through the nose, whether we do an open approach. And in fact, my partner prefers to do all these through cranial facial resection.

When I say a cranial facial resection is an open craniotomy, there's a lot of different flavors of how you'd do that, but repair with a pre-parochial graft with endoscope assistance. And we do, Dr. Choby and myself, do have a preference. If we believe we can get negative margins, to do that all through the nose and do a multilayered reconstruction.

But I want to emphasize that even though that's our preference, if we cannot achieve negative margins, we will convert to a cranial facial resection. And we will sometimes break towards doing a cranial facial resection if we think we're on the edge, just because it's a more efficient way to get a margin negative resection. And that is the most important thing about the surgery.

Dr. Garret Choby:

Yeah. And also, just for our listeners who may largely be otolaryngology trained, realize that the endoscope is simply a tool to do a job. And at the end of the day, doing the job properly is what's most important. So, a margin native status is the King in this tumor surgery. So, whatever it takes to get that as is what's most important for the patient.

Dr. Jason Barnes:

So, say this is a resection that's able to be done endoscopically through the nose. What does your resection look like? And can you talk a little bit about the reconstruction?

Dr. Garret Choby:

The first thing I'll mention is that I think every operation is tailored towards the individual tumor. So again, presuming we're doing endoscopic endonasal resection, let's say it's a fairly typical tumor that we see. We'll typically get everything opened up from orbit orbit, frequently with a draft three frontal sinusotomy, as well. And open up both widely such that the entire skull basis is open to us, and we can see orbit the orbit.

We'll do our bony osteotomy, usually with a drill. Again, tailored for that individual tumor. And again, depending on how much intracranial involvement in orbital bulb and track involvement will matter a bit about what dural and extended margins that we take. We'll clear that with frozen section interoperative markers, and we oftentimes will send many, many, many frozen sections, pathologists probably hate us a little bit, but it's worth it.

Dr. Jamie Van Gompel:

And you should.

Dr. Garret Choby:

You should.

Dr. Jamie Van Gompel:

I mean, everywhere you are, you should be biopsying in quadrants. And in fact, to the skull base, probably breaking that up into eight different segments to make sure that you have a margin negativity, because it is that important.

Dr. Garret Choby:

And then again, assuming we're doing an endoscopic cranial facial resection or an anterior cranial resection, we would tend to lean towards a multi-layer reconstruction. We usually like a large fascial autograph as an inlay. Sometimes even Duralgin above that, synthetic dural eye insets. And then at the outset, we'll raise a very large extended nasoseptal flap to be in the case.

We'll routinely check the septal margins on that to ensure we're clear of tumor as you make those cuts with our Bovie, that's tucked in the nasal pharynx for the surgery. And then once we're done and the fascia lata has been in place, then rotate up and cover the entire skull base from frontal sinus orbit to orbit to plenum.

Dr. Jamie Van Gompel:

I'd say most commonly, we don't have a nasoseptal flap to work with for these cases. And we will do a two layer repair with separate layers of fascia lata, one inlaid, and then one laid against the periorbital. That's been, all the bone has been removed from that. And there is a price to be paid for that kind of reconstruction. There's a lot of nasal debridement that needs to be done long-term when you don't have nice vascular tissue. And in some circumstances, those are the patients that people really believe, should we add in a pair of cranial graft on them, and people are converting more commonly to doing cranial facial resections for those.

Dr. Jason Barnes:

And if patients didn't have radiation therapy before surgery, is it routine to have it done post-operatively?

Dr. Jamie Van Gompel:

So, the board answer is yes, most of the radiation literature supports that. There are centers such as ours, that with the margin negative resection and low Hyam's grade pathology, we will reserve or give the patient option for no radiation. Now we just published on this, this year, where in those patients that chose not to have radiation, there's a higher chance of recurrence compared to what is more aggressive pathology.

But the salvageability is very good for those patients. And what we looked at mostly is, what is the real cost of that radiation? And honestly, we're talking about radiating the frontal lobes and a very de-mucosalized nasal vault. The overall morbidity is probably very low, and this gets back to what the patient's preferences is, but most people are electing for radiation nowadays.

Dr. Jason Barnes:

What about chemotherapy?

Dr. Jamie Van Gompel:

So, chemotherapy is reserved for metastatic disease, currently. There is no adjuvant therapy for post-operative radiation, it's only neoadjuvant for preoperative. There's nothing to suggest anything out there that we're going to sensitize this with any particular agent. What is also pertinent, I think, to the discussion is some people try, so there was a period of time when people were trying to boost margins that were positive with Gamma Knife, and that's been shown to not really have the same outcome as patients with margin negative resections.

Whether or not proton beam plays a role in here is largely unknown, because a that's new therapy. So, realistically, that decision of proton beam versus IMRT Classic with photons should be reserved to the radiation oncologist in the likelihood of long-term secondary diagnoses like malignant brain tumors, or meningiomata from that radiation. And most commonly, patients under the age of 50, probably nowadays, if they're lucky enough to be at a proton beam center, we'll probably opt for that because of that reduction.

But there should be no difference in outcomes in those two, terms of the immediate therapy. This tumor has a long potential for people to live for a very long time. So, it's important to consider the secondary toxicity of the radiation.

Dr. Garret Choby:

I agree a hundred percent. I think I'll mention, with your question about chemotherapy is that again, reserved for metastatic disease. But we published a series early this year, where in some folks who, again, were not able to achieve a margin negative status at the outset of planning their procedure, may get neoadjuvant chemotherapy or combined with radiation therapy in order to get them to a surgical resectable lesion. So, that is our potential for chemotherapy in the neoadjuvant setting, in order to shrink the tumor to give us a margin negative resection.

Dr. Jason Barnes:

And we discussed that there's maybe 5% of folks who have a neck mass, what is the role for treating neck disease?

Dr. Garret Choby:

This is a little bit controversial, but most literature supports not performing an elective neck dissection, if there's no clinical disease present. Because again, about 95% of patients won't have a node at that time. Now, as Dr. Van Gompel mentioned, this is a disease with a certain amount of longevity to it. So, there is a fairly high rate of delayed neck metasticies.

There's a multicenter study, a few years back, looking at about roughly 10 years after their initial surgery. Ann roughly 15% of people would end up getting a delayed neck node at some point along the way. Here, we have to resalvage them with a neck dissection, although radiation will be an option as well.

There are some centers that do elect to perform elective neck radiation in any patient undergoing treatment for a session or a blastoma. Their thought is that it may reduce the risk of a neck node popping up later on. But I would say that's still pretty controversial right now.

Dr. Jamie Van Gompel:

It's fairly controversial. But you know, it will be good to see that data. I want to mention though, that having a single positive neck node is the number one indicator for mortality from this disease. So, any single time they have that, it's a different actor.

Dr. Jason Barnes:

And can you speak a little bit more to how you counsel your patients regarding surgical complications or you know, what to expect after surgery, but also prognosis?

Dr. Jamie Van Gompel:

So, once we have all the data, I think it's important for us to have that discussion. We don't usually make that off the frozen section inter clinic because the Hyam's grade will change sometimes with a larger tumor sample. But it's going to be broken into, obviously their Kadish stage, their Hyam's grade, and also if we achieve margin negative resection.

But we're expecting a lot of these patients to live a long time. The median survival is about eight and a half years for these patients, and we have that discussion. It's hard to tell any individual patient with the lack of a large series on this, what their outcome will be. And we tell them that we're going to settle them for the long haul. That's how I manage this.

Dr. Garret Choby:

Yeah, I agree. Now I will also echo the same sentiments, but I'll add that I think, just to reemphasize, the Hyam's grade does matter. So, in a pretty large SEER database study, folks with a Hyam's grade one or two had about a two thirds, 10 year survival. Where the Hyams grade three or four had only about a 30-35%, 10 year survival. So, that does make a difference, and it's something we'll counsel our patients on as well, as far as the Hyams grade, the aggressiveness of it.

Dr. Jason Barnes:

And after surgical resection, how do you follow up with these patients?

Dr. Jamie Van Gompel:

So we, in the first year, get a scan at three months, six months, and then yearly for a period of time. But the real important thing is that the nasal endoscopy is a very important tool, and we can't sit back and

rely on just the MRI to guide us. I mean, it's more common at least if you look in the literature and this may be biased a little bit, but I see recurrences with endoscopic examination.

A clinical neck exam is still very important in these patients. Although one of the issues, of course, is that the most common lymph node involvement is the retropharyngeal lymph nodes, which isn't typically felt obviously with the clinical neck exam. We don't routinely follow them with PET unless they have high grade disease at the outset, and they have margin positive disease.

Dr. Garret Choby:

I'll also mention, as far as in the immediate post-operative period, we usually will do a first debridement, one to two weeks after surgery, if we're doing a true craniobase resection, there's not much in the nose to support nasal packings. In those cases, which is unusual for us, we usually will use things like MRSA sponges that need to come out. And debride them a few more times with that first month or two to make sure they're healing well, make sure there's no CSF leak, et cetera. And that'll set us up well without scarring, then monitor them long-term with nasal endoscopy.

Dr. Jason Barnes:

Awesome. Thank you all so much for being here. I do want to provide a brief summary. But before I do, anything else worth mentioning that we didn't talk about?

Dr. Garret Choby:

I'll just mention the importance in treating these tumors with an experienced multidisciplinary team. So, it's otolaryngology, it's neurosurgery, it's radiation oncology, medical oncology pathology. Everyone's really, really important with this pretty rare disease process. So, I think it's a key thing to have a good team you can trust and work with.

Dr. Jason Barnes:

Great. Well, thank you so much. I will do a quick summary here. Esthesioneuroblastoma typically presents with more ENT symptoms like nasal congestion, nasal obstruction, maybe sinusitis symptoms, but can also have symptoms like headache, possible visual impairment, and about 5% of folks present with a neck mass. When you evaluate these patients, you might see a fleshy mass on nasal endoscopy towards the cranial vault.

Pathophysiology includes the fact that it's a neuroblastoma from these olfactory cells. And one of the buzz words that you might hear on pathology or the Homer Wright Rosettes, and this is classified as one of those small round blue cell tumors. Workup includes CT to identify skull base erosion. An MRI might classically be described as having a dumbbell appearance, but that's not always reliable.

Biopsy should be considered in clinic. And these tumors have different grading systems. One is the Kadish, which describes where the tumor is. And then there's the Hyams grading system, which describes the histopathology, and metastatic disease should be considered. Treatment can involve neoadjuvant radiation therapy before surgery, but surgical resection plays a large part in this treatment paradigm.

And follow up with these patients is essential, both in clinic and with imaging. And as Dr. Choby said, depending on Hyams grade, prognosis can be more promising than the higher Hyams grade. Anything else worth adding?

Dr. Garret Choby:

No. Thanks for the time.

Dr. Jason Barnes:

Yeah. Thank you.

Speaker 4:

Thank you.

Dr. Jason Barnes:

It's now time to bring this episode to a close, but before we do, I'll run through some questions. As always, I'll ask a question, wait a few seconds before answering it to give you time to pause or consider the answer, and then I'll give the answer. So, the first question is, what are the most common presenting symptoms of esthesioneuroblastoma, and what percentage present with a neck mass? The most common presenting symptoms of this tumor are things like congestion, nasal obstruction, and possibly epistaxis or other sinusitis like symptoms. But we can also see headache, rhinorrhea, hyposmia, and neck masses are seen in about 5%.

Next question, describe the Kadish grading system. The Kadish grading system is split into four parts, A, B, C, and D. Type A is confined to the nasal cavity. Type B is extension into the paranasal sinus. Type C is tumor beyond the nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of skull, intracranial cavity, and orbit. Type D is meds to cervical lymph nodes or other distance sites.

For the next question, what does another classification system on histology that can have an impact on prognosis? This is the Hyams grading system, which is a histologic classification to describe the grade of the tumor. And finally, what is the standard treatment for this tumor and how do we follow up with it? These tumors almost always require radiation and surgery. Sometimes radiation is better before surgery and sometimes it's used afterwards. And in terms of follow-up, patients should have close follow-up, especially with nasal endoscopy to be evaluating for any recurrence, and follow up MRI also plays a large role in this. Thanks so much for listening and we'll see you next time.