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If you’re new to NETWise, we strongly recommend you go back and listen to the first episode in this series. It will give you a solid grounding in the basics of neuroendocrine tumors and how they’re treated. And you can find a whole library of episodes on different topics at netrf.org/podcast, and wherever you get podcasts.

Do you have a story to tell about your own NET journey? If you’re a NET patient who would like to participate in a future episode, please email us and let us know! podcast@netrf.org

Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. I’m Jessica Thomas, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

NETs are often rare, complex, challenging to diagnose, and difficult to treat. Some of the rarest, most complex, challenging and difficult NETs are known as pheochromocytomas and paragangliomas. They’re frequently referred to as “pheos and paras.”

Today, we’re devoting a whole episode to these tumors. This is an updated version of an episode that first came out in 2021.

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A pheochromocytoma is a NET of the adrenal gland. The body has two of these glands, one on top of each kidney. They are responsible for producing hormones that help regulate the immune system, metabolism, blood pressure, stress and other essential functions.

There are two main parts to the adrenal gland. There’s an outer part, called the adrenal cortex, and an inner part, called the adrenal medulla. Each part produces different hormones. A pheochromocytoma begins in cells in the *inner* part of the adrenal gland.

A paraganglioma develops from the same type of cells as a pheochromocytoma, but it occurs *outside* the adrenal gland. That might be in other parts of the abdomen, the pelvis, or the head and neck. Sometimes these tumors are called extra-adrenal para-gang-liomas.

Dr. Lauren Fishbein is an Endocrinologist at UCHealth and the University of Colorado School of Medicine.

**Fishbein:** *“If they're inside the adrenal gland, it's called a pheochromocytoma. If they form in one of the nerve bundles outside from the skull base, all the way to the pelvis, those are called paraganglioma. So paraganglioma and pheochromocytoma look exactly the same under the microscope – can't really tell them apart. So they're just named differently based on whether they're in the adrenal gland or outside the adrenal gland.”*

These tumors are very rare – fewer than 3,000 people are diagnosed each year in the United States. Only around 15% of those cases are cancerous.

These tumors tend to be slow-growing, but it can be difficult to accurately determine how a given tumor might behave.

With other kinds of NETs, a pathologist can examine the physical characteristics of tumor cells to determine how aggressive the tumor is. This is called a tumor’s “grade.”

But with pheos and paras, the usual rules don’t apply.

Here’s Dr. Joseph Dillon, an Endocrinologist at the University of Iowa:

**Dillon:** *“The grading system, which is what the pathologist sees, is quite different from the grading system for neuroendocrine or carcinoid tumors of the pancreas or small bowel. I don't think the grading system is really as well worked out in pheochromocytomas and paragangliomas.*

*You cannot tell when you remove a paraganglioma or a pheochromocytoma whether it's going to eventually spread or not, so you can’t actually tell based on the pathology whether it's truly benign or not.”*

While these tumors tend to be slow-growing, some do behave as high grade tumors. Particularly with paragangliomas: while some grow so slowly that they can just be observed, others are aggressive and need immediate treatment.

Another characteristic that sets paragangliomas apart is that they have a tendency to develop multi-focal primaries. This makes it difficult to determine whether multiple paras are one primary tumor and its metastases, or multiple primaries that developed independently of each other.

**Dillon:** *“Yes, you can have a primary paraganglioma that then metastasizes to somewhere else in the body, but you can also have the issue of multiple paragangliomas occurring either at the same time, or are at different times over, over their lifetime. It's sometimes very difficult with a paraganglioma when you see a scan to say this tumor here is a metastatic tumor versus this is multiple primary paragangliomas.”*

Both paragangliomas and pheochromocytomas can be “functional” tumors. This means they actively secrete excess hormones into the body.

Like we mentioned earlier, the adrenal glands produce hormones. Specifically, they produce hormones related to our “fight or flight” responses. These hormones are epinephrine – also known as adrenaline, — norepinephrine, and dopamine. These kinds of hormones are called “catecholamines.” All pheos, which are in the adrenal gland, as well as a good percentage of paras, produce catecholamines.

Dr. Nancy Sharma is a Medical Oncologist at the Swedish Cancer Institute in Seattle, Washington:

**Sharma:** *“Even if people are not symptomatic, based on the amount of catecholamines being produced, they still are functional. They will still have catecholamine release.”*

An excess of these kinds of hormones can cause a wide range of severe symptoms. Think about it: higher than normal levels of fight-or-flight hormones coursing through the body are going to have an effect.

**Fishbein:** *“Think about how you feel when someone comes up behind you and scares the bejesus out of you – you feel it, you feel kind of a surge in your body, right? Sort of energy coming up.*

*Patients with pheochromocytoma can have levels of adrenaline that can be two times the upper limit of normal to fifty times the upper limit of normal. So there can be really high levels of adrenaline that don't go away.”*

These symptoms can include high blood pressure, headaches, heart palpitations, anxiety, nervousness, or panic attacks.

Samantha Greenberg is a Genetic Counselor at the University of Texas Southwestern Medical Center:

**Greenberg:** *“What’s unique to these tumors is that people have persistently high blood pressure, even on medications, even in other settings.”***Dillon:** *“Blood pressure that's difficult to control. So people who get diagnosed with blood pressure perhaps at a younger age – they get on one agent, two agents, three agents, four agents for their blood pressure and their blood pressure is still poorly controlled. That can be driven by adrenaline.”*

An excess of adrenaline can also cause mental and emotional symptoms that can be difficult to manage.

Sometimes the increased level of adrenaline is relatively steady, which causes a persistent feeling of stress and anxiety. It can also surge periodically, causing episodes that can feel like panic attacks.

**Dillon:** *“So sudden onset of heart racing, sweating, pounding headache, pounding chest – which we call palpitations – shakiness, and indeed a sense of true anxiety lasting anywhere from five minutes to fifteen to thirty minutes.”*

Some people can experience these symptoms as anger.

**Dillon:** *“It can certainly cause people to have to have a sense of rage and lash out. There are people who have ended up in court or in psychiatric facilities and eventually get diagnosed as a person with a pheochromocytoma.”*

As you might imagine, misdiagnosis like this is not uncommon.

Bonnie Bennett is Nurse Coordinator for the Neuroendocrine Tumor program at the University of Pennsylvania.

**Bennett:** “*A lot of the patients will be misdiagnosed for many years with anxiety disorders, different psychological… maybe even suicidal, we've had patients who were suicidal because nobody can figure out what's wrong with them.”*

Something that can help doctors finally reach a diagnosis is genetic testing. Up to 40% of patients who have a pheo or para have a genetic predisposition.

You can hear more about the relationship between NETs and genetics [in episode 13 of this series](https://netrf.org/podcast/episode-13-nets-and-genetic-screening/).

Pheos especially are strongly connected to some of the genetic conditions we heard about in that episode, including M.E.N. 1 and 2, Von Hippel Lindau Syndrome, and SDH gene mutations.

**Bennett:** *“Of all of the tumor types there are for cancer, Pheochromocytoma and paraganglioma have the highest association with genetic syndromes, genetic causes of any other tumor type.”*

**Fishbein:** *“Especially because it is rare, and so it's not always thought of as the first diagnosis. If someone presents with anxiety, rage, or anger, we think about depression and anxiety as the more common diagnoses, and those are going to be the more common diagnoses. But we have to consider that if it's associated, maybe, with high blood pressure, if it's associated with an already known predisposition syndrome, like VHL or MEN2, then we have to think about pheochromocytoma as well.”*

**Soto:** *“So my name is Eli Soto. I'm currently coming to you from Fort Collins, Colorado. I'm 43 years old. So, I was diagnosed with a stage three metastatic pheochromocytoma. It was on my right adrenal, and it metastasized to the retroperitoneal cavity, to the lymph nodes. And I am coming up, almost… this summer will be two years of remission.*

*You know, the Pheo just kind of sneaks up on you. You know, this is a type of disease that is insidious in every part of your life, but it's like a frog boiling in water. That's the best way I can put it. You know, it happens so slowly over time that you don't know you’re in any real danger until it's a big, giant problem inside you.*

*It was one day where I was building a closet and I was going back and forth from upstairs to my garage. And I was leaning down trying to get my miter saw off the floor. I pressed my knees into my chest and I strained trying to get it up off the ground. And in that moment… I don't know if you ever see the movies where somebody gets, like, injected with adrenaline and you hear the boom, boom, boom, boom, you know, the heartbeat and everything? Well, that's what I could hear inside my body. I could, it felt like a rising tide. It felt like blood pressure or any kind of pressure was just rising from my chest to my neck. And then all of a sudden there was a huge explosion in the back of my brain.*

*Now, one of the things that I hate about the literature right now is they refer to one of the symptoms as severe headaches. That's like getting your foot cut off and saying ‘my foot hurts.’ It doesn't do it an accurate description. For the listeners out there, I think the best way to describe one of these events is if you've ever seen the movie ‘Alien’ with Sigourney Weaver – do you remember how the little alien pops out of the chest cavity? That's what it feels like in the back of your head. It feels like something is trying to get out of the back of your head. So I remember grabbing the back of my head, falling on the ground screaming. That was the most intense pain I have ever felt in my entire life.*

*And as fast as it comes on, this “boom, boom, boom, boom” adrenaline rush and this explosion, this feeling like you're about to die, you can't speak to anybody during that time. It's so painful. It goes away almost as quickly as it comes on, as if it never happened. You can get up and just walk it off, as if that moment never happened. It’s the weirdest thing.*

*Then that week, it just started to get worse - the frequency of it just started to get more and more and more until one night, it just happened when I was just laying in bed, just not doing anything. And I told my wife at the time, I was just like, ‘Listen, something's not right. I got to go to the hospital’. I made it to the hospital. I remember holding on to the front desk. And that's when I had another event, just a huge explosion. I fell backwards. I just remember it being back in the ER and they were cutting my clothes off, and they did every test possible that night.*

*So when I went back to go speak with the neurologist after the blood and the urine, he said, ‘Eli’, he said, ‘the amount of catecholamines you have in your system today is the equivalent of doing crystal meth every day of your life’. So you can imagine what I must have been like to be around.*

*And I look back and, you know, there's a lot of things that I'm not proud of and just the interactions with work colleagues, personal family issues and everything like that. I didn't have a lot of patience. I was constantly anxious. Like, you know, I was nervous about the world around me. Edgy, agitated. Towards the last three years, I only slept two hours a day. You know, that in itself makes the mind go a little bit, kind of crazy, you know? And it's significant how much it affects your personal life and the relationships around you.”*

After a long period of misdiagnosis, Eli’s pheo was finally removed surgically. Since then, he hasn’t needed treatment, and the hormonal changes to his mood and personality have disappeared.

*“Everybody that knows me that’s still in my life from before and after tells me how different I am right now. They're like, ‘We all notice it’. Like, ‘You're, you're not the same man you used to be at all, and much more pleasant to be around.*

*I feel like I feel in the moment, in the present, I feel fine now. There’s always that fear in the back of my head that's like, you know, anytime I have a bad day or, you know, I get agitated with somebody, that's my first go-to thought like, ‘Oh my gosh, is this coming back? Did they miss something?’ If it does come back, knowing what I know now, I feel like I'm at the forefront of all the access to all the research that's been done – just the level of care that I would need to get to get this out of me – that even if it does come back, I know I'll be in good hands.”*

When it comes to treating pheos and paras, the best first option is usually surgery.

**Dillon:** *“As a general rule, the only curative treatment for pheochromocytoma or paraganglioma is a surgical removal of the tumor.”*

**Fishbein:** *“And so once we make the diagnosis, we find the tumor on imaging and make the hormonal diagnosis, then surgery is the mainstay of therapy.”*

When pheos or paras are functional, and causing hormonal symptoms, there are some precautions that need to be taken for surgery. This is because surgery can cause additional adrenaline spikes.

So, before a patient with a functional pheo or para is operated on, they have to be treated with medications called “alpha blockers” that mitigate those adrenaline rushes. This medication is usually given for about two weeks before a surgery.

**Fishbein:** “*Anesthesia, the surgery itself, cutting into the skin, these are physical stressors where a normal body response is to increase adrenaline. And so, if you already have a tumor that has high adrenaline, and now it's going to go even higher, we worry about a hypertensive crisis where the blood pressure gets so high it could lead to a heart attack or stroke. And so that's the reason to give this alpha blocker medicine before any surgery so that we can block those receptors as best as possible. And then during the surgery, the anesthesiologist will use similar alpha blocker medicines through the IV to help control that as well, because we don't want any adverse outcomes from the high adrenaline level during surgery.”*

This doesn’t just apply to surgery: a patient with a functional pheo or para may need alpha blockers before any kind of medical procedure that may cause physical or mental stress.

**Bennett:** *“Any procedures, like if they go to the dentist, they may need blocking because they have this low level of catecholamine release from their tumors, and we don't want them to have a problem when they go for a procedure. So, if they're going to have a colonoscopy, any type of procedure, they need surgical blocking.”*

This is also true for the diagnostic process — something as simple as a biopsy can have dangerous effects.

**Dillon:** *“One of the problems with diagnosing a paraganglioma and pheochromocytoma is that one of the things that can cause a pheochromocytoma to actually produce a hormonal surge is sticking a needle in it for a biopsy.”*

**Bennett:** *“If someone is in a car accident and they go for imaging and the imaging shows something on the adrenal gland, that should never be biopsied, because if it's a Pheo and your blood pressure shoots up, you would be at risk for having a heart attack or stroke. So radiologists should know that if there's something worrisome there on the adrenal gland or extra adrenal in a location where paragangliomas are known to be found, they should not be biopsied.”*

Once this prep work is done, surgery can be safely performed.

With pheos, the tumors which occur within the adrenal gland, there are two main options: option one is total resection, where the entire adrenal gland is removed. Option two is partial resection, where some of it is left intact. The choice has to do with how likely the cancer is to recur.

Dr. Nancy Perrier is Head of the section for surgical endocrinology at MD Anderson Cancer Center in Houston, Texas:

**Perrier:** *“We’re going to want to start planning that operation to resect the tumor, but to do so in a way that leaves the least amount of morbidity in the long term, so we’re always taking those risk/benefit ratios.”*

We have two adrenal glands, one above each kidney, and if one remains in place, the body can function normally. If both are removed, the patient will need hormone replacement therapy to make up for what their adrenal glands are no longer doing.

So if doctors think the surgery will be curative, they might recommend a *total* resection of the adrenal gland that has the pheo growing in it. If there’s a chance that a pheo might grow on the *other* side, they may opt for a partial resection.

**Perrier:** *“The adrenal gland is like a boiled egg, a little boiled egg that sits right on top of the kidney, and a pheo is a tumor that arises in the yolk of the boiled egg. But the adrenal gland has a function for the white and a function for the yellow. So if we're trying to remove the tumor and let's say that was, you know, a cherry or a plum that was growing out of the yolk, our goal would be to remove the yolk and that plum, but to leave a little piece of the white boiled part of the egg and just the white, so that that patient would then have the hormone and would not need hormone replacement for the cortisol, which is made from the boiled white of the egg.”*

It might sound counterintuitive, but a total adrenal resection is a quicker and simpler surgery than a partial resection.

**Perrier:** *“It’s easier just to take out the whole boiled egg, right? It's intact. It has good margins, and it doesn't fracture. If you have to start getting into carving the tissue and making sure that it doesn't fracture and whatnot… but if you're just gonna scoop and just take the boiled egg out, that can be quite easy. And so for a patient, when we're not worried and we know that that other gland is going to be fine, that can be a simple, easy operation.*

*A paraganglioma doesn't arise in the adrenals, so there is no role of saving any portion of that. The decision-making has different branches, but it's not partial versus total resections, always total resection”*

For many pheo/para patients, one successful surgery may be all that is needed.

But recurrence can happen, sometimes many years later, so an annual screening is recommended.

**Fishbein :** *“For most people with pheo/para, surgery is curative. We still recommend that everyone gets followed for life if they've had a pheo/para at least once a year, to just make sure there's no recurrence or another primary multifocal tumor.”*

People who have a genetic syndrome associated with these tumors are particularly prone to recurrence – and their family members should also be screened.

**Greenberg:** *“When somebody has a paraganglioma or a pheochromocytoma identified, they need genetic testing to know if there is some kind of hereditary cause for that mutation, which as we've talked about can impact both treatment and family members. Once somebody has that mutation identified their family members also need genetic testing, which is typically a saliva or a blood sample to identify if they have that same genetic change that's previously been found in other relatives.*

*After that, if somebody tests positive for a mutation, regardless of whether or not they have a tumor history, they require screening. And that screening is what we would consider to be high risk screening, which means you have an increased risk for these tumors, and we need to do imaging and blood work, or a urine sample, to identify whether or not you might have these tumors. And the goal of that screening is to identify those tumors early so that we never get to the point where patients have signs or symptoms of these tumors, but rather that we're able to identify them resect them, or monitor them without impacting the patient's quality of life.”*

In cases where the tumors do recur, further surgeries can often be the best option.

**Perrier:** *“Yes, (it’s) not uncommon that repeat surgery is a part of the lifelong management of these patients.”*

However, sometimes surgery isn’t an option, or isn’t sufficient to manage the disease.

**Sharma:** *“Of course surgery is the cure, but we know that up to 10-15% of Pheos and more of Paras – up to 30% of Paras – can be malignant, and they can come back, sometimes several years down the lane. And a lot of time, if they come back, and they are metastatic and local therapies are not an option in that situation, then we do get involved for systemic therapies.”*

There are a few non-surgical options for treatment.

The first is PRRT, or “Peptide Receptor Radionuclide Therapy.” [You can learn more about PRRT in episode 28 of NETWise](https://netrf.org/podcast/netwise-episode-28-prrt-revisited/). Essentially, the treatment uses a synthetic version of the hormone somatostatin to deliver a radioactive isotope to the tumor in a targeted manner.

PRRT was FDA-approved in 2018 to treat other kinds of NETs, but it does not have FDA approval for treating pheos and paras.

Because these tumors often have somatostatin receptors, PRRT can be an effective form of treatment, and has been used off-label for a handful of years.

**Dillon:** *“These tumors very frequently – 80, 85% of them – will have somatostatin receptors. So PRRT, intravenous radioactive somatostatin, will stick to the tumor, bring the radioactivity into the tumor.”*

Between 2018 and 2023, there *was* an FDA-approved treatment on the market for unresectable, metastatic pheos and paras. This medication was called Azedra. It used similar technology to PRRT, delivering radioactive isotopes to the tumors with a synthetic analog of the hormone norepinephrine.

But in 2023, the company that manufactured Azedra announced it was taking the medication off the market. Here’s Dr. Erik Mittra, Chief of Nuclear Medicine and Molecular Imaging at Oregon Health and Science University in Portland:

**Mittra:** *“ So the most obvious other option would be the other radiopharmaceutical systemic treatment, which is peptide receptor radionuclide therapy, PRRT.*

*The main thing I will mention right off the bat about it, though, is that it is not FDA approved for pheochromocytoma/paraganglioma. So the use of it, which has been happening for as long as the Azedra has been used because it was also approved in 2018, is technically off-label.*

*And you know, we use a variety of different medications off-label in medicine. But it always needs to be a little bit more cautious because what that means is there isn't as much evidence in terms of efficacy for that particular type of tumor. And then also it can cause insurance issues because since it's not FDA approved, an insurance company can potentially deny it.”*

Beyond these radiopharmaceutical treatments, there are a few other options as well.

**Sharma:** *“There are targeted therapies – tyrosine kinase inhibitors, sunitinib has traditionally been used. There are newer trials with cabozantinib, the multi-tyrosine kinase inhibitors, axitinib, and also everolimus is being tested. Chemotherapy has been used in circumstances also.”*

But medicine is constantly evolving, and there are always new things on the horizon.

There’s a study underway at the National Institutes of Health that is treating pheo/para patients with PRRT, which has the brand name Lutathera.

**Mittra:***“It's specifically to evaluate the utility of Lutathera for pheochromocytoma and paraganglioma. As mentioned, you know, people have been using this off-label for a long time, but we need rigorous data to be able to actually know, first of all, what the true efficacy and toxicity of it is, but also we would ideally need that data to be able to expand the indications of Lutathera to include pheochromocytoma and paraganglioma.*

*And then that will hopefully allow the FDA to include pheochromocytoma and paraganglioma and the revised package insert for Lutethera.”*

This study is currently in the recruitment phase, and results are a few years away.

But no matter what the options are, there’s one treatment decision that’s more important than any other, and it’s this: find a care team that specializes in these tumors.

This is a very rare, very subtle, and very complicated cancer, and working with experts can make a huge difference.

**Dillon:** *“These are very complex tumors. It is truly important for patients to find physicians and physician groups that have an expertise and an understanding of the different dimensions of this type of tumor.”*

**Greenberg:** *“When I talk to new patients, a lot of the biggest things that we talk about is how important it is to have a multidisciplinary care team. When we sit down every month at our pheo/para high-risk clinic tumor board, there is a surgeon there and an oncologist there, and an endocrinologist there. Our research team is present. The nurse that helps us run the clinic is there. I'm there as a genetic counselor, and we all contribute to the care of this patient. And it's really important because in pheo/para realm, there are so many different needs, right? If you're going to resect a tumor, you may also need to have an endocrinologist involved for the proper blocking prior to surgery. And that requires both a surgeon and an endocrinologist. So, I think having a multidisciplinary team is really crucial, especially when we think about inherited risks, because these tumors can pop up in different parts of the body. So it's important to have somebody who is a head and neck specialist and somebody who's a urologic specialist and somebody who's a cardiothoracic specialist involved in your care team to make sure that as things arise, you're at a place that has a lot of experience and also is able to talk between the silos of specialties to coordinate care in a really multidisciplinary way.*

*When something is rare and complex and complicated, you want to make sure that you're somewhere where they know what they're doing, and they've seen it before, right? You want to make sure that when you talk to a provider, you're asking, how often do you do this? Because the more that somebody has experienced in it, the better off that your outcomes are likely going to be.”*

**Perrier:** *“This is not the role of an occasionalist. There are just too many nuances and the comprehensive care of the patient is critical. What should I do? What should I take into consideration? What discerning factors for the possibility of following this patient for a lifetime, and for them living in harmony with this disease.”*

Thanks for listening to NETWise. I’m Jessica Thomas, Director of Patient Education for the NET Research Foundation.

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