THE LACNETS PODCAST

With Jaydira Del Rivero, MD

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Transcription:

Lisa Yen
Welcome to The LACNETS Podcast. I'm your host, Lisa Yen. I'm the LACNETS Director of Programs and Outreach, as well as a caregiver and advocate for my husband who is living with NET. In each podcast episode, we talk to a NET expert who answers your top 10 questions. This podcast is for educational purposes only and does not constitute medical advice. Please discuss your questions and concerns with your physician.

Thank you for joining us for today's episode of The LACNETS Podcast. I'm pleased to introduce our featured speaker for today, Dr. Jaydira Del Rivero. Dr. Del Rivero is the endocrine oncologist at the National Cancer Institute at the NIH. Dr. Del Rivero is board certified in both endocrinology and oncology. And as we know, neuroendocrine tumors and in particular paragangliomas and pheochromocytoma involve both these disciplines of endocrinology and oncology. So she's able to bring together both perspectives in her research and clinical care, and we're very grateful for that! Dr. Del Rivera's current efforts is the development of novel treatment approaches and targeted therapies for endocrine malignancies such as Advanced gastro-entero pancreatic neuroendocrine tumors, adrenal cortical cancer and pheochromocytoma and paraganglioma. Dr. Del Rivero serves on the Board of Directors for NANETS (the North American Neuroendocrine Tumor Society) which is the NET professional medical organization that we would like our doctors to be on so that they can network with others in the NET field. And she serves as an NANETS Guidelines Committee co-chair and is one of the authors of the NANETS consensus guidelines for the surveillance and management of metastatic and/or unresectable pheochromocytoma and paraganglioma. Last, but certainly not least, Dr. Del Rivero is a dear friend of LACNETS and she serves on our newly-formed Medical Advisory Council. So we're glad to have her as part of the family. Thank you for joining us again on our LACNETS Podcast.

Dr. Jaydira Del Rivero
Thank you so much, Lisa and LACNETS, for giving me this opportunity to talk to you all about pheochromocytomas and paragangliomas. As you said, this is something that is very dear to my heart and something that as part of our efforts at the National Cancer Institute, we also try to develop better therapies and more therapies for pheochromocytoma and paragangliomas, and we are fortunate here at the NIH that we have well known endocrinologist, Dr. Karel Pacak, who is a world expert on

pheochromocytoma and paraganglioma. We work very closely together and we also have treatment studies for pheochromocytomas and paragangliomas as well as other neuroendocrine tumor. So thank you so much for having me today. I'm very excited to be here today with you all, and I hope all of the questions and answers here are useful to our pheochromocytoma and paraganglioma community. LACNETS is also an organization very dear to my heart because of all of the efforts that you're doing to educate our patients with neuroendocrine tumors. So thank you. I'm really grateful to be here with you today.

Lisa Yen
We're excited to have you and thank you for your dedication. Just out of curiosity, how did you get interested in not only are the rare disease of NET, but in a rare subset of a rare disease?

Dr. Jaydira Del Rivero
As you said earlier, I am board certified in endocrinology and oncology. When I started, I first did my endocrinology fellowship. And when I started my endocrinology fellowship, I worked very closely with Dr. Pacak here at the NIH and I started learning about pheochromocytomas and paragangliomas during my fellowship. Then I practiced as an endocrinologist in New York City under the guidance of Steve Libutti who is also well known in the neuroendocrine tumor field. And at that time, we were building the endocrine oncology program as part of Albert Einstein. And at that moment, I realized the need of developing better therapies for not only for pheochromocytomas and paragangliomas because back then there was not FDA approved agents, but also for neuroendocrine tumors. As we all know, in the last decade, there has been a lot of advancements for the management of neuroendocrine tumors. I think we are hopeful now because a lot of experts in the field but also the motivation that we have to develop other therapies for neuroendocrine tumors, including pheochromocytomas and paragangliomas which are considered also neuroendocrine tumor. But it was back then, when I was practicing endocrinology, that I felt that there was a need to develop better therapies and with the guidance of Dr. Steve Libutti, I decided to come back to the NIH and I did a second fellowship. And my institution is very supportive and very encouraging as well to study rare cancers and to be able to develop better therapies for neuroendocrine tumors, including pheochromocytomas and paragangliomas. This was a long answer, but the short answer to your question is that based on the need to develop better therapies, I wanted to dedicate my whole time but also my life to develop better therapies for these tumors, and I hope in my lifetime we can hopefully find a cure. That's my hope. I think everybody's hopes, too.

Lisa Yen
We all hope the same. Thank you for seeing the need and stepping up and really doing something about it. It really makes those of us in the field who live with NET, and then I'm sure especially those who live with a rare type like para and pheo, feel seen. Thank you for helping people feel seen.

Dr. Jaydira Del Rivero
Thank you.

Lisa Yen
So again, we're just gonna have a conversation about one of your favorite topics, paragangliomas and pheochromocytomas. As we get started in this, I'm just wondering if you might just explain for the audience, who should be listening to this podcast episode? And do all NET patients need to know about para and pheo?

Dr. Jaydira Del Rivero
I think since this podcast is focusing on pheochromocytomas and paragangliomas, I do feel that patients that has this suspicious for these tumor type or is living with pheochromocytomas and paragangliomas should definitely listen to this podcast. Moreover, I have to also mention here that LACNETS also has videos describing what pheochromocytomas and paragangliomas are, and also the management of advanced disease. I think LACNETS has wonderful libraries of information that also mention pheochromocytomas and paragangliomas, not only in English, but as well as in Spanish. And I think it's important that patients that live with pheochromocytomas and paragangliomas listen to the LACNETS library. Moreover, we have the Pheo Para Alliance as well who has a lot of information dedicated also for pheochromocytomas and paragangliomas. Also I have to say that since pheos and paras are neuroendocrine tumors, I just want to make sure that our audience are well-educated, not only to learn about disease, but also to educate others living with this disease, as well. I think knowledge is power so this is important as well.

Lisa Yen
Knowledge is power. Well said! And yes, we just want to acknowledge that there are other resources out there like you said, not only the videos that you did for us but of course The Para Pheo Alliance, who are our friends and they have quite extensive resources, virtual conferences, support groups and meetings to help those living with para and pheo. So let's get into the first question. What is paraganglioma and pheochromocytoma? Is it a type of cancer? And how common is it?

Dr. Jaydira Del Rivero
Let's just discuss what are pheochromocytomas and then paragangliomas. Overall pheochromocytomas and paragangliomas, as we sometimes call it, pheo para or para pheo, to include both of those tumors, that the reality is the same. When we look under the microscope, it's the same tumor type, but the location is different. Pheochromocytomas and paragangliomas are rare neuroendocrine tumors and they produce an excessive amount of a hormone called catecholamines or metanephrines. Pheochromocytoma forms in the adrenal medulla. So I always like to describe that the adrenal glands are on top of each kidney. And if we were to cut the adrenal gland in half, you have the other layer of the adrenal gland which is called the adrenal cortex, but then the inner layer of the adrenal gland is the adrenal medulla. And that's where the pheochromocytomas form. Paragangliomas originates from nerves outside of the adrenal gland, and it could be anywhere from the head, chest, abdomen and pelvis. But the reality is when you look under the microscope it's exactly the same. And another name for the paragangliomas are also called extra-adrenal pheochromocytoma because it's outside of the adrenal gland. A little bit more to describe between pheochromocytomas and paragangliomas, most of the cases are pheochromocytomas, about 80 to 85% are pheochromocytomas. But approximately 25% of these pheos and paras are paragangliomas. I also like to mention that in terms of where it's located, they can be different type of paragangliomas. They are the paragangliomas that are located in the head and neck. I don't want to get too complex but sometimes we call those parasympathetic paragangliomas. And the reason why we wanted to make a difference is because these head and neck paragangliomas, most of the time are nonfunctional, or nonsecreting. That means that they don't produce hormones. And we can talk a little bit later about what the excess of hormone is and what symptoms they may cause related to the excess of hormones. But also we have the paraganglioma that are located anywhere from the chest, abdomen and pelvis, most of the time they are functional or secreting, meaning that they can produce an excess of hormones and they can cause symptoms because of those hormones. Most pheochromocytomas and

paragangliomas are functional, as well. But I think it's important to differentiate in terms of where they're located and what is the difference between pheochromocytomas and paragangliomas. As we discuss this mainly the location, whether they are in the adrenal gland or outside of the adrenal gland. As we discussed, the most common is the pheochromocytomas, about 80 to 85%. And we discussed that approximately 20% are paragangliomas. We also discussed the paragangliomas are the head and neck. Most of the time, they're not functional or not secreted. And then we have the paragangliomas located anywhere from the chest, abdomen and pelvis. And they usually secret catecholamines as well. The other question that you mentioned is whether this is a cancer. Most pheochromocytomas are considered benign, which means that they are not cancer. And what that means, because I also like to discuss what is the definition of cancer. Cancer is a condition in which some of the cells make growth uncontrollable and they can spread to other parts of the body. And because of that, what we means that whether pheochromocytoma is a cancer, is when the pheochromocytomas spreads in other parts of the body. And that's usually the definition of cancer. But I have to mention that as I say earlier, most pheochromocytomas and paragangliomas are benign, but approximately 10% of the pheochromocytomas can be malignant, and approximately 25% of paragangliomas can also be malignant, as we discussed, malignant or cancerous because it can spread to other parts of the body. So in terms of how common it is, is considered a very uncommon type of cancer, a rare cancer. So approximately, we say in terms of the statistics is that two to eight people per every 1 million people are diagnosed with this tumor type. So we can see it's very rare. So anywhere from two to eight per 1 million people may be diagnosed with these two tumor types. So it's very, very rare, based on the statistics.

Lisa Yen
Wow, thank you for that very thorough answer. Just like with all NET, it sounds like location matters. Where it's located really has a lot to do with everything else, the rest of the conversation you're going to be having. And in terms of benign versus malignant, that has to do with if it's spread, that would be malignant, versus if it's not spread that would be considered benign. And so cancer is defined as if it's already metastasized. So what do you call if it's not spread? Is it not a cancer?

Dr. Jaydira Del Rivero
So yes, so that's very good question. So as I discussed earlier, what makes the definition of a malignant or cancer, there are certain findings that when looked into the microscope, that makes us believe that these could have a greater risk of metastases, but at the same time when these tumors have the capacity to go to other places, so that's what we call malignant and as I said earlier, most pheos and paras are considered benign, meaning that they don't have any findings that have a higher risk of malignancy. And I have to say that there are certain criteria even though there has not been any score that has been validated in order to tell me whether these tumors has a risk of metastasis or not, but there are certain things that when you look under the microscope, whether there is any invasion or whether these cells necrosis from when we look at in the microscope, and the cells are many death cells, whether also how the morphology is looking under the microscope that make us understand whether these tumors may have a risk of metastasis or not. So paragangliomas, meaning the extra adrenal pheochromocytomas, a lot of these paragangliomas may be associated with a genetic mutation and this situation succinate dehydrogenase mutation. Genetics are important in pheochromocytomas and paragangliomas. So that's the reason why every patient with pheochromocytomas and paragangliomas needs to be seen by a genetic counselor, because approximately 30 to 45% of these pheochromocytoma and paragangliomas are hereditary, meaning that they may have a germline pathogenic variant, meaning that they can be in every cell in the body. That's what germline say when

they can be in every cell in your body and you can then transfer that mutation if you were to have a kid. So there is a possibility that your kid may have that mutation, and when a patient have that mutation, they may have the risk to develop tumors. Because of that, there is a mutation called succinate dehydrogenase mutation type B that has a higher risk of having a malignant behavior. So that's the reason why whenever there is a patient that has pheochromocytomas and paragangliomas needs to be seen by a genetic counselor to run a panel of what we call cancer predisposition syndromes, genes that cause cancer predisposition syndrome to then guide us on what will be the follow up for those patients. What we're trying to prevent is having these tumors diagnosed late or having the appropriate follow up and screening and surveillance scans, and prevent those tumors for going to other places. We talked about different aspects so I just want to make sure that it's very clear to our audience, what that means. And I think just to go back a little bit, you asked the question about whether if pheochromocytoma is localized, whether it's malignant, or whether it's going to other places. So as I said earlier, most of pheochromocytomas and paragangliomas are benign, there is a small risk of these tumors to become malignant, meaning that they can metastasize. Now, one other aspect we're still trying to learn is that if the patient has a pheochromocytoma and paraganglioma, who has the greater risk of metastasis? And one of the risks that we mentioned is, for example, the size of the tumor. So if any paraganglioma that is more than four or five centimeters in size has a risk of metastases. The same with pheochromocytomas, which is an adrenal gland, the size is important whether that could have a greater risk of metastasis. Also, looking under the microscope to see whether there is an invasion or an lymph node involvement, or whether there is any necrosis or cell death that can also give me an idea whether they can metastasize as well. We talked about the genetics as succinate dehydrogenase mutation, especially SDHB ("b" as in boy) has a greater risk of metastasis as well.

Lisa Yen
Thank you for that. And that's a perfect segue. I know you already started answering questions about is it genetic, and who should get the genetic testing, which you said everyone should, and they would get the genetic predisposition panel. I'm curious, when should they get genetic testing, if there's a certain time?

Dr. Jaydira Del Rivero
This is a very good question. So every patient, the minute that they're diagnosed with pheochromocytoma, or a family member who is diagnosed with this cancer predisposition syndromes, that's when they need to have genetic testing. Let me just go back a little bit here. So the question was, who gets genetic testing? As I say, every patient that is diagnosed with pheochromocytomas and paragangliomas needs to have genetic testing. Also, if there is a patient that had one of these genes associated with cancer predisposition syndrome, those patients also need to get genetic testing as well. And the reason is that there are different hereditary syndromes associated with pheochromocytomas and paragangliomas. Just to mention a few, we have the multiple endocrine neoplasia Type 2A or Type 2B. So the reason why is because Type 2A versus Type 2B have different clinical presentations. For example, the Type 2A is associated with another neuroendocrine tumor of the thyroid gland, which is called medullary thyroid cancer, also pheochromocytomas mainly in the adrenal glands rarely paragangliomas meaning outside of the adrenal gland, and also the Type 2A is also a benign tumor of the parathyroid gland which is located in the thyroid gland. That's the reason why it's called parathyroid and that gland is responsible to regulate the calcium in the body. So that's 2A. 2B besides the medullary thyroid cancer and the pheochromocytoma have very specific physical findings, that's called Marfanoid habitus meaning they're very tall or lanky, sometimes their arms are bigger. So there are certain physical findings that are associated with multiple endocrine neoplasia Type 2B. So whenever

we see somebody, sometimes we see this Type 2B that sometimes hasn't been diagnosed before, we call that de novo. But sometimes based on the clinical findings, make us also suspicious of this Type 2B. So the gene affected for either 2A or 2B is the RET proto-oncogene. So, for example, the neurofibromatosis type one. So the gene associated with that is NF1. They also have a very specific tumor presentation, the NF1, they have the neurofibromatosis, meaning they are the skin finding too. They have the optic gliomas; there are certain tumors in the back of the eyes as well as the cafe au lait spots. So there are certain characteristics with NF1 that make us suspicious and the gene affected is the NF1 gene. We also have other cancer predisposition syndrome called von Hippel-Lindau. Von Hippel-Linadu also has a very specific tumor associated with von Hippel Landau and the gene affected is the VHL gene. And we have the hereditary paragangliomas, and those are the succinate dehydrogenase mutation, either A, B, C, or D. Most common of those is either the B or the D. I know that I said a lot right now, and I apologize for saying so much. But I think it's important. just to summarize, every patient that have pheochromocytomas and paragangliomas need to have a genetic counselor, and also needs to have a panel specific for pheochromocytomas and paragangliomas. It's possible that there may be a sporadic, meaning that we don't know the cause of the pheo para, but we're able to diagnose one of these genes associated with pheochromocytomas and paragangliomas and also it can guide us in what will be the follow up as well what kind of scans we need to do, what surveillance scans we need to do. Based on the cancer predisposition syndrome, there are guidelines as well that can help us determine what will be the follow up. At the same time, if we find someone that has one of these mutations associated with a cancer predisposition syndromes that can also guide us to test also family members or the kids. So that's the reason why so important.

Lisa Yen
Sounds like key information that we need to know or that you need to know about your patients. Thank you. That's very helpful. And you also answered, which naturally would come up, if family members should get tested or screened.

Dr. Jaydira Del Rivero
Yes, it's very important. I just want to mention something because genetic counseling is important and can sometimes be a little bit confusing too because there's always a patient that was diagnosed with pheos and paras and usually ask me who needs to have genetic counseling. All patients diagnosed with pheochromocytomas and paragangliomas need to be referred to a genetic counselor. We discussed that approximately 30 to 40% are hereditary. But also once we know that information, it can help us get surveilance in patients and their families, but also help us to establish the risk to understand whether they can develop another pheochromocytomas or paragangliomas in other parts of the body. It can also help us guide who may have a recurrence or a risk of metastasis. As well as I discussed earlier with a different cancer predisposition syndromes, help us to establish the risk of other tumor associated with that cancer predisposition syndrome.

Lisa Yen
Yeah, so key information that you need to guide so many things here in terms of the whole conversation, not just the treatment, but gives you a better picture of the landscape. Our next question is a very common one, what are the symptoms of para or pheo?

Dr. Jaydira Del Rivero
We know that paragangliomas, for example, the head and neck that do not secrete any hormones, and then we have the paragangliomas which can be localized anywhere from the chest, abdomen or pelvis,

as well as the pheochromocytomas, the majority of them produce hormone, and because they produce these hormones, they can also develop these symptoms. And just to let you know that diagnosis of pheochromocytomas and paragangliomas, especially with symptoms, they also call it, "The Great Mimic," because it can have a series of symptoms, and some of them may not be very specific. And because of that, some patients with pheochromocytomas or paragangliomas may be misdiagnosed. Sometimes they may have high blood pressure, and they think like, well, maybe it's just any essential hypertension that can happen or sometimes because of the palpitations or feeling anxious, they may also be confused of having depression or anxiety. So I think it's important that we explain the symptoms related to pheochromocytomas and paragangliomas. Some of them may be chronic, so these symptoms may be happening for some time.

Lisa Yen
It sounds very unfortunate and frustrating that they could be misdiagnosed for many years.

Dr. Jaydira Del Rivero
That's correct. And sometimes we have seen patients that have had all these symptoms for long periods of time, and they don't know that this could be a pheochromocytoma or paraganglioma. By the time we see them here in our institution, they already have metastatic disease. So I think awareness about these tumor type as well [as an] increase in education that you can think about these tumor whenever we have this specific symptoms is important as well as. And educate our healthcare providers if somebody has the symptoms to think about the zebras. That also happened with other neuroendocrine tumors as well. There are especially neuroendocrine tumors of the GI pancreas, over the years they're diagnosed with irritable bowel syndrome without thinking what we can do next right, and then get treatments and doesn't get better. So I think that it's important to acknowledge the different symptoms associated with this tumor type. We discussed about the high blood pressure. So the high blood pressure is something that we see in patients with this excess of hormones. Also palpitations, meaning the heart rate is elevated.

Lisa Yen
So when you mentioned high blood pressure, how high is high? How high would make you think this might be a para pheo?

Dr. Jaydira Del Rivero
That's a very good question. Because patients with high blood pressure, they can have very elevated blood pressure, meaning when the systolic blood pressure, the highest number can be in the 180s, for example, it could be quite high. At the same time, we could also see fluctuations in the blood pressures, sometimes very high, and sometimes it goes very low depending on the amount of hormones that the tumor is producing. And also sometimes in regards to the blood pressure, there are certain things because these elevated blood pressure and the palpitations and the sweating, these episodes sometimes can happen several times during the day. And there may be certain things that can also precipitate what we call these "pheo spells." Sometimes these crisis because the blood pressure can sometimes go very, very high, and when it goes very high, sometimes they can cause bleeding in the brain, sometimes it can be associated with some cardiovascular events like a heart attack. So I think it's important to understand when the symptoms happen and what can also precipitate these exacerbation of symptoms. And I want to mention this because I think it's important to know that there are certain stress that can also precipitate this pheo spell or crisis. Sometimes some patients are diagnosed with a pheochromocytoma when they need to have a surgery for other unrelated issue. And then when they

go to the OR, trying to do surgery, the blood pressure goes very, very high, or the anesthesia can precipitate those events as well. Also, there are others pain as well, or trauma or severe stress. There are certain foods or drinks that may also exacerbate some of these crisis. For example, cheese or bananas, or even a high amount of caffeine. Other certain drugs, for example, that can precipitate this crisis, the steroids. Sometimes we take steroids because of back pain, we have a car accident, and sometimes we need to have steroids and sometimes that can also precipitate this crisis as well. So I think that's also something that we need to keep in mind whenever that happens we need to then guide us like, oh, well, maybe this could be a pheochromocytomas and paragangliomas. The question is, when do we suspect there may be a pheo para? The signs and symptoms related to these hormone access. Also, when there is an increased blood pressure, either by drugs as we discussed or certain drugs. Cocaine can also do that, amphetamines can also do that whether there is anesthesia or surgery and that we see this elevated blood pressure. Whenever we see this variability in the blood pressure either very high or very low. Sometimes when we have someone that is very difficult to control blood pressure, and sometimes we see patients that have like four or five different antihypertensive medication and sometimes it's very difficult to control that can also help us suspect that this could be a pheochromocytomas and paragangliomas. So there are certain things that we need to keep in mind so that way we don't have this misdiagnosis as we unfortunately see in a lot of our patients,

Lisa Yen
Thank you for that very thorough answer, just the awareness of what might be causing these hormonal symptoms, basically, and then blood pressure fluctuations as well. And as you called it, "The Great Mimic," because it can be vague and easy to miss. I think it's very interesting, these blood pressure fluctuation, headaches, diseases, these are all vague symptoms, and you're mentioning that a lot of times this is found incidentally or accidentally. Now shifting to testing and screening, what scans should I get if I have para or pheo? And is there a certain order to which the scan should be done?

Dr. Jaydira Del Rivero
First, we need to establish the diagnosis of pheochromocytomas and paragangliomas. I mentioned earlier when to suspect a patient with pheo para, about the signs and symptoms related of catecholamine. I didn't mention earlier that I hope to take the opportunity to mention here is that we discussed the blood pressure and the sweating and the palpitation but there also can be other symptoms like anxiety, pain on the chest, feeling very fatigue. Sometimes heat intolerance can be one of those symptoms very rarely as well. Constipation, that's another one because the excess of hormone can definitely cause constipation too. Sometimes changes in position, as well, we can see variability on the blood pressure as well. Weight loss, as well. The excess of hormones can also impair your insulin production in the pancreas, and that means that sometimes they can cause diabetes. We see these very elevated blood glucose as well. Flushing is another one as well that we sometimes see with these patients. There are a series of symptoms that can be associated with pheo para. So as I discussed earlier, first, how do we make the diagnosis of pheochromocytomas and paragangliomas, we have these various signs and symptoms. We discussed the elevated blood pressure caused by certain events like surgery or anesthesia or variability on the blood pressure. So another thing when to suspect pheo para, when there is a person of family history associated with pheochromocytomas and paragangliomas. We discussed earlier about the different cancer predisposition syndrome. With all those signs and symptoms, that can help us suspect about pheochromocytomas and paragangliomas then we need to make the official diagnosis. So how? First, we need to do the biochemical evaluation. I think prior to doing a CT scan, sometimes I have to say that pheo paras are diagnosed incidentally for other reasons. They have CT scans, they have an accident and they need to have a CT scans, and

that's when we see these findings as well. But it's important also to establish what we call the biochemical diagnosis and that's usually with a blood test. And as we like to obtain the blood, what we call the metanephrines in higher than normal amounts is a sign of pheochromocytomas and paragangliomas. Sometimes we do a 24 hour urine collection. It can be a blood test or it could be a 24 hour urine collection as well. But then once we have the biochemical diagnosis that is suggestive of pheochromocytomas and paragangliomas, then we need to do the scans. What kind of scans do we need to do? We usually recommend obtaining a CT scan, or computed tomography scan, or it can also be an MRI or Magnetic Resonance Imaging. These are the type of scans that help us to obtain a detailed pictures of what is inside the body. Now something that I want to mention is that for the head and neck sometimes we prefer to obtain the MRI because sometimes it's more detailed than the MRI, and because in the neck area we have many structures in the neck, the MRI may be better for the head and neck paragangliomas. Also if somebody's pregnant and we suspect a few pheochromocytomas and paragangliomas, an MRI is absolutely better because there is no radiation with the MRI. But a CT scan is also very helpful to help us diagnose the location. So where it is a pheochromocytoma, whether it's a paragangliomas, CT scans and MRIs can also be very helpful.

Lisa Yen
This is really helpful to establishing the diagnosis. So you said first, you start with biochemical evaluation. Let's break that down. What labs should be done first before moving to the scans?

Dr. Jaydira Del Rivero
So there are either a plasma or a urine test. I hope I can explain this because sometimes I get this question, what is the difference between catecholamines versus metanephrine, and I hope I I can explain it well to our audience. If there is any further question, please go back and look at the LACNETS video on pheochromocytoma and paragangliomas because there is a figure there about what these different tests are. But let's explain in terms of the hormonal evaluation, of the test specifically for pheochromocytomas and paragangliomas. So we have what we call the catecholamines, and the catecholamines is three hormones that are measured within the catecholamines, and the catecholamines consists of epinephrine, norepinephrine, and dopamine. Now, the other ones that we measure is the metanephrine. Epinephrine is then metabolized to metanephrine and the norepinephrine is metabolized to normetanephrine and then those are your metanephrines. So we have your catacholamines and then you have your metanephrines. Now metanephrines are the best test to do in the plasma. And the reason why is because your catecholamines. The half life of catecholamines is shorter, and sometimes we can miss a pheochromocytoma if you only measure the catecholamine. It's very important that we measure the metanephrines, what we call the most sensitive scans. And those are the ones that we mentioned the plasma. We also have the 24 hour urine collection of either catecholamines or the metanephrines. Sometimes the 24 hour urine collection can detect, because as we discussed earlier, these pheos can be very episodic, and sometimes may not be when we see these episodes of the pheochromocytomas and paragangliomas, sometimes on occasion may not be measured in the blood, and sometimes we need to do a collection of 24 hours of urine because that's throughout 24 hours. And sometimes they're able to also detect some of those spells. And sometimes that can give us a lot of information. But usually we start with the plasma (the blood tests) because we feel that that's the most sensitive test and it's usually the plasma metanephrines. If there are any questions, I feel like you can also watch the LACNETS videos because there is a picture there about what means by catecholamines and metanephrines, and I hope you find that useful.

Lisa Yen
Yeah, that is a beautiful slide to refer to. And then you were talking about scans, and predominantly either CT or MRI based on location, or if there's a possibility of pregnancy. With a CT, is there a certain type of CT that should be done? As you know, I know with NET, there are certain types of CTs. CT with contrast can definitely gives us a lot of information. Of course, if there is something suspicious in the liver, MRI is always better for the liver. Magnetic Resonance Imaging is always better for the liver, whether it is a GI pancreas neuroendocrine tumor, or whether it is a pheochromocytoma. If we want to look at the liver, the MRI is better. But CT scans with contrast is always very, very good for the diagnosis of pheochromocytomas and paragangliomas. Sometimes there is a CT scan specifically for the adrenal gland if it's only a localized adrenal mass or adrenal gland. Sometimes there is a specific dedicated CT scan of the adrenal gland because, depending on when they inject the IV contrast, sometimes we need to understand what is the certain measurements within the CT scan with contrast. We call that the Houndsfield units. And again, I'm sorry if I'm saying too much of the technicality. Sometimes there's a specific scan of the adrenal glands to help us understand whether it looks more benign, or whether it looks more like a pheochromocytoma or something of more of malignant. So the CT scans are important, but again, there are specific CT scans of the adrenal glands that help us differentiate whether this has benign versus not benign. Thank you for that. So CT with IV contrast, or MRI, if it's in the liver, or possibility of pregnancy, or CT dedicated adrenals. And what about any functional imaging?

Dr. Jaydira Del Rivero
That is a very good question. Especially pheochromocytomass and paragangliomas are types of tumors that like to be imaged by functional imaging modalities. So when do we do functional imaging modalities? Functional imaging modality is either a 64-copper dotatate scan, or a 68-gallium dotatate scan, or we also have the MIBG scan. Those are the types of functional imaging modalities. Here at the NIH, we have other functional imaging modalities that's called the F-dopa scan, but that's considered research and is only here at the NIH. Commercially, the dotatate scan or the MIBG scan is available. And the reason why I'm saying this is because pheochromocytomas and paragangliomas, approximately 95% of these tumors may express the somatostatin receptors on the surface of the cell, and that's why dotatate scan is becoming a very, very good scan of functional imaging study for this tumor type. So what is the indication of a functional imaging study? This is all paragangliomas. Even if it's less than four or five centimeters in size, any paragangliomas need to have a functional imaging studies. And the reason why I'm saying that is because sometimes the paragangliomas can be in multiple places, especially the ones associated with a succinate dehydrogenase mutations. It can be in other places. So the functional imaging, like the dotatate scan, can be very, very helpful. Any pheochromocytoma that is greater than five centimeters in size is also an indication to do a functional imaging modalities. Because size is important. The greater the tumor, the greater the risk of metastasis. Any patient that has a recurrent pheochromocytomas or paragangliomas needs to have a functional imaging studies, as well as any patient that had metastatic disease. It's important to do a functional imaging study because it helps us to do the complete staging of the tumor. And also any suspected pheochromocytomas or paragangliomas that doesn't have any symptoms, too. Another scan is the MIBG scan, and we do that scan in patients with metastatic disease. And the reason why is because there is MIBG treatment. The MIBG treatment was approved in 2018 for metastatic pheochromocytomas and paragangliomas. So if we feel that there is a patient that may benefit from MIB therapies, it's important to do an MIBG scan. Now, sometimes the question that I get, and I know because sometimes insurance is difficult to prove both the MIBG scan and dototate scan. I think for staging we'll prefer the dotatate scan, because that has a very good scan to stage, to look to see what

tumors we can find in the body. Sometimes not all pheochromocytomas and paragangliomas may be positive on MIBG scans, so that's the reason why I feel that dotatate scan is the best functional imaging modality. Now, we think about treatment. So I will say to do an MIBG scan because the MIBG therapy is the only treatment approved for pheochromocytomas and paragangliomas. But not all patients are positive on MIBG. Approximately 45% of pheos and paras are positive on MIBG scans. The majority of patients with pheochromocytomas and paragangliomas may be positive on dotatate scan. But there are some of them that may not be and that's why we need to use other scans such as the glucose scans, FDG PET scan or even the F-dopa scan. But I don't want to mention that because it's really for research and is not available, and is not going to be approved by insurance.

Lisa Yen
Thanks for also explaining, not just which scans, but the priorities if insurance is causing issues. I'm wondering if it matters what order people get the scans? Do they need to start out with a CT and then get a dotatate scan or vice versa?

Dr. Jaydira Del Rivero
Once we have a patient that is diagnosed wiht pheo para, if it's localized on the CT scan, unless, like I said, all paragangliomas need to have a functional imaging modalities because it can be in other places in the body. And unless the pheochromocytoma, meaning the tumor in the adrenal gland is greater than five centimeters in size, because we know that the greater tumor, the greater the risk of going to other places. If this is three or four centimeters, maybe that patient doesn't need dotatate scan or MIBG scan. But any patient that has metastatic disease, they need to have functional imaging modality after the CT scan. And my preference will be to start with a dotatate scan because that is the most sensitive scan. Approximately 95-98% of pheos and paras can be seen on the dotatate scan in terms of the number of tumors. You can see that it's a very good scan. MIBG is not all of them; 45-50% may be seen on the MIBG scan. But yes, I think any patient that we feel may have metastatic disease risk or a risk of metastatic disease, we need to have a functional imaging modality, like in this case, a dotatate scan.

Lisa Yen
So now we have a diagnosis. We started the workup with labs and imaging. What's the treatment for para or pheo?

Dr. Jaydira Del Rivero
If it's localized, then we need to do surgery in those situations. Whenever we have a localized pheochromocytoma, as I said earlier, most common in terms of the pheo paras is a pheochromocytoma in the adrenal gland, if it's localized, surgery is indicated. If it is sporadic, meaning that there is not any known cause or cancer predisposition syndrome associated with pheo para, after the tumor is resected, it's very important that we check the hormones after surgery, usually anywhere from four to eight weeks after surgery. But I like to follow those patients every year for life because there is still a risk of recurrence. So that's important to know. Now, if there is a paraganglioma, after repeating the hormonal evaluation after surgery, when it's localized, we'll resect it. In those situations, I still like to follow the hormonal evaluation every six months or every 12 months. And in those situations, if it's a paragangliomas or it's associated with one of the cancer predisposition syndromes that we discussed, I like to obtain either a CT or MRI every two years depending on what gene or mutation is associated with the pheochromocytomas and paragangliomas. And of course, pheos and paras are associated with either von Hippel-Landau or NF-1 or the MEN 2A or B that we discussed earlier, there are certain imaging studies of protocols that is according to the guidelines for those cancer predisposition

syndrome. Just to summarize, if it's localized, surgery. The issue is when it's metastatic or when it is localized but we are unable to resect. And that's when we need to discuss other therapies. Lisa, do you want to discuss the management of metastatic disease?

Lisa Yen
Please share some of the options, and I think the the biggest questions are, how do I know how to get appropriate treatment? How do I get appropriate treatment? And how do I know what appropriate treatment is?

Dr. Jaydira Del Rivero
Like I said earlier, once it's localized, surgery, there is a specific follow up for those patients. But once it's metastatic, or it's locally but is unable to resect it, that's when we need to understand what we need to do next and what my options are. Prior to that, I want to mention something that I didn't mention that is super, super important is any patient that is undergoing surgery, or any patient that has metastatic disease that may require a certain treatment, it's important for those patients to have a medication with an alpha blockade, either doxazosin or phenoxybenzamine just to mention some of them. And the reason why is every patient that is pheo para that is secreting needs to have these types of medications. Alpha blockers, sometimes they may [also] need a beta blocker such as propranolol, metoprolol, that's the other medications that they have. But these excess hormones binds to some receptors on the blood vessels. So when there's this excess hormones and going binds to the receptors in the blood vessels that can cause what we call vasoconstriction and the blood pressure can go very, very high. So because of that, we need to give a medication that blocks those receptors. So that way, it doesn't cause the high blood pressure. And it's important because we discuss some of the risk of having these elevated blood pressure. But yes, it's important, very important. Every patient that is either undergoing surgery, or they're going to have systemic therapies or any procedure with the diagnosis pheo para that is secreting hormones, always, always alpha blockers. Doxazosin, phenoxybenzamine. And phenoxybenzamine is very expensive. It's not widely available, most common is doxazosin, prazosin, terazosin, those are called the "zosins." And in some situations for the headaches, and for the high blood pressure too, adding a beta blocker sometimes can have a benefit, but it's always first alpha blocker and then the beta blocker, because if you give the beta blocker first and you don't know that they have the diagnosis of pheochromocytomas and paraganglioma that can definitely cause an elevation of the blood pressure. So now we discussed the management to help block this hormone excess. We discuss alpha and beta blocker. Now what do we do when it's locally advanced and we cannot do surgery when there are distant metastasis? I think it's important to understand what treatment options we have. And in a subset of patients, I'm not saying all of them, but there may be some patients that may benefit for some surgical intervention or local therapies even on the metastatic setting. But that's the reason why needs to be discussed with a multidisciplinary team or surgeon that is very familiar with this tumor type to understand what will be the benefit of resecting some of the tumor even in the advanced metastatic setting, especially for the patients that secrete hormones. But in the setting of metastatic disease, meaning in different parts of the body, what I like to understand as someone who treats this tumor type is whether it's slow growing or whether it's rapidly growing. So it's very important whenever I see a patient with pheochromocytomas and paragangliomas that is metastatic, I need to understand what is the disease growth, because based on that it can guide me on what will be the treatment that I will recommend. We have a patient where the tumors are growing quite rapidly, there are a lot of tumors that I see in the body, and they're symptomatic because of that, maybe chemotherapy is what I would recommend. And there is a specific regimen that we recommend in those situations. And the regimen is with a chemotherapy with three different chemotherapy agents,

cyclophosphamide, vincristine, and dacarbazein. Now when these are slow grade, moderate grade, moderate progression, either slow, moderate progressive disease, but it's still metastatic, first I need to determine whether you know, I can give other therapies. MIBG is a type of radiation therapy, that can be a good option for those patients that have MIBG positive tumors and also for those patients that the hormones are high and is causing these symptoms, because that's how it was initially approved. The MIBG treatment, it was approved, because the patients that received treatment, they were able to decrease the blood pressure medication by 50%. And I think that's something that was very important because their blood pressure got better and they decrease the amount of medications blood pressure medicine that these patients were receiving, and that's how the MIBG treatment was approved. And if the patient has, MIBG-positive tumors and they are secreters, that could also be a very good therapy. Sometimes the question that I get is when to we give Lutathera? Lutathera is approved for patients that have GI and pancreas neuroendocrine tumors. And it makes sense if my tumor is positive on the dotatate scan, can I get Lutathera treatment? And it can. I have to say that it's an ongoing clinical study for Lutathera, for the treatment of advanced metastatic pheochromocytomas and paragangliomas. Sometimes because it's not approved by the FDA for that indication, sometimes insurance is difficult to proven for that, but we have a clinical study. I think it's important to consider participating in a clinical study. But there are other treatments as well in the metastatic setting. And we have those family of drugs called tyrosine kinase inhibitors, and those are drugs that block the blood vessel supply going into the tumor. And these tumors are very vascular, it makes sense to give one of those treatments. But that's something that we need to discuss with the physician who is treating you what my options are, and when to give it. I think it's important. Some of these tumors may not grow and that's why we need to understand and it's okay in those situations, and we just want to watch it just to see how they're doing, what we call observation in some patients may still be beneficial. To summarize, the alpha beta blockers are certain medications to block the hormone excess. Now, we need to understand whether it's locally advanced. Surgery may not be indicated for distant metastases. We need to establish what is the growth rate because if it's rapidly growing and there are many tumors, chemotherapy may be the option. If it's growing, but slow-paced, we need to consider some of these radiopharmaceuticals Lutathera or MIBG. MIBG is the only FDA-approved agent. Lutathera in the setting of clinical trials. We discussed other options like the tyrosine kinase. One thing to keep in mind is that sometimes these tyrosine kinase can increase blood pressure and that's what these medications do so that's why it's even more important to make sure that we control your blood pressure with these medication that was discussed, the alpha beta blocker. And some patients may benefit from surgical intervention, even in the metastatic setting. But we need to discuss that with our surgeons and see where the risk and benefit. It's not for everyone, but that's something that we need to discuss. And again, if it's not growing, and it's not causing any symptoms, observing may be an option. But I think those are the options that we need to discuss based on how the tumor is behaving, based on how many tumors we have in the body. And those are the things that we need to consider. And that's why sometimes I feel like these tumors needs to be discussed with someone who has expertise on these tumors, because that can definitely help us understand and guide treatments based on what is the growth rate, if the tumor is positive in MIBG or in dotatate scan, how many tumors we have in the body, and what are the treatment options.

Lisa Yen
What an excellent overview really explaining well this is not an easy decision, it's very complex, and as you said, you need a multidisciplinary team and a multidisciplinary approach to weigh in all these various factors especially with metastatic disease to see what is the best option. And of course, you're looking at a multiprong approach, both with the symptom management with the alpha blocking, and

then also the tumor control with anything from watching and learning to chemo to Lutathera or PRRT or oral agents. Many options out there, I think that's the takeaway. There's not just one or two, there are many possible options available even with metastatic disease. And that's hopeful and encouraging. So the next question is, what if I had surgery and my disease recurs after surgery? What are the treatment options then?

Dr. Jaydira Del Rivero
Yes, and that's why there is an indication. If you have the tumor, the tumor was resected and recur, that's also an indication to do a functional imaging studies to make sure we don't have any tumors any other place in the body, and we discussed in those situations, we like to use the dotatate scan, either the Copper-64 or the 68-Gallium dotatate, it's the same. Sometimes a patient is like what do I do, which one is better? But it's the same. The same for other neuroendocrine tumor is the same. I will just say that whatever the scan is in your facility, I think that's the answer. The two of them are equally the same in terms of how they're able to diagnose the tumors. But if it recur, we need to know where it recur, whether it recur in the area where the surgery was. Sometimes the reason why it recur is because sometimes there are, even after the surgery, there may be some tissue left behind, sometimes because there is involvement of the lymph nodes. So that's why looking under the microscope, looking at the pathology findings is important, because if we know that there is some lymph node involvement, we know that there is an invasion in those areas where the surgery was, the likelihood of recurrence is high. So first is to determine if it recurs, if it's localized, whether another surgery will be beneficial. So that's something that we need to discuss with our patients. Whether any type of local therapies can be done, if surgery is not an option and it's still localized in one area. And then of course, the functional imaging modality is very important to determine whether there is another part of the body because when it's another part of the body, then we need to discuss the systemic therapies that we discussed earlier.

Lisa Yen
So, if it reoccurs, and it's localized, surgery could be an option again. That comes up frequently, can I have surgery again? Or as you said, maybe other localized treatments. And then if it's spread, based on functional imaging, then we go back to the options you mentioned previously.

Dr. Jaydira Del Rivero
Yes, that's correct.

Lisa Yen
The next question is, after surgery or any other treatments, will my symptoms be gone?

Dr. Jaydira Del Rivero
Usually, when it's localized and we resect all tumor, symptoms tend to go away, because you removed the tumor that is producing the excess of hormones and without this excess of hormones, you may not have the symptoms, right? We have seen these in our patients. They have all the symptoms like high blood pressure, the sweating, the heart palpitations, and once that tumor is removed, the symptoms are gone. We have seen that. Now, when we have tumor in other places, metastatic, even if you did surgery, but if you have tumors in other places that may produce the hormones, it's possible that you may still have the symptoms associated with the pheochromocytomas and paragangliomas. To recap, yes, if the tumor is localized and we resect all the tumor, symptoms tend to get better. But if it's in other places, then symptoms may not necessarily go away. So that's why it's very important the indications of

when to do this CT scans or MRI or the indications of when to do the functional imaging modalities to help us understand if there is any other tumors any other part of the body.

Lisa Yen
That's hopeful that hopefully the surgery or treatments would help people feel better. And so the last question, say I'm someone who has para or pheo and I've been told I can't get a biopsy, or that surgeries might be dangerous, what do I need to know? And what do I need to do?

Dr. Jaydira Del Rivero
That's the reason why your alpha and beta blockers are so so important, especially for the tumors that are secreting the hormones because that can help us control the symptoms related to the hormone excess. So if we suspect that a patient has pheochromocytoma and paraganglioma, and sometimes we have some difficulty controlling this hormone excess, we sometimes don't necessarily like to biopsy this tumor because the minute that you start putting a needle in the tumor that can release these hormones and with these hormones we have all these symptoms. But if a biopsy is indicated, we need to make sure that the patient has adequate alpha blocker, as well as sometimes plus minus a beta blocker. So when you to make sure that the blood pressure is controlled under those medications before a biopsy is done. So that's very important because we don't want a patient to have a biopsy that doesn't have the adequate blocker because once you start putting a needle in the tumor and mobilize the tumor, that can definitely cause the release of hormones. And that release of hormones can definitely cause all the symptoms that we discussed earlier. So I think that's important. that prior [to] any surgery, that the patient is an adequate Alpha blocker plus or minus beta blocker, depending on what symptoms we need to control.

Lisa Yen
And just to clarify, how do we know if it's adequate blocking?

Dr. Jaydira Del Rivero
Because sometimes with these excess of hormones, we see these fluctuations in the blood pressure. So once I see that there is not that much fluctuation on the blood pressure, and sometimes my patients may say to me, I was in the 90s and then on the 170s, and they tell me, it's more stable, I don't see that much fluctuation and the medication helps to do that. Also, when we see those changes in the blood pressure with posture, we call that postural changes relate to the blood pressure, that indicates maybe it's enough of alpha blocker in that situation. Sometimes we recommend the patient to take extra salt in those situations. Sometimes we give salt tablets to avoid those postural, what we call hypotension, meaning that changes in the blood pressure when sitting. So I understand that sometimes it can be a little bit confusing, because sometimes they say, well, my blood pressure is high, so I cannot take any salt, but once you have adequate blockade, and we don't see the much fluctuation on the blood pressure, and we see that there is some postural changes in the blood pressure, we can recommend to the patient to keep an eye on it and we may need to give you a little bit of salt. So that way, if we don't see that much change, sometimes with the phenoxybenzamine, patients feel a lot of stuff. They feel a little fatigue, those are one of the side effects as well. Sometimes I want to keep an eye as well. But sometimes when we see that I think you have adequate alpha blockade. But yes, that's an important question. So when do we see an adequate alpha blockade and what to do once we feel that there is an adequate alpha block, and we see what we call postural hypotension, meaning changes in the blood pressure with posture. So in those situations, we do recommend adding a little bit of salt, either in the diet or sometimes giving your salt tablets.

Lisa Yen
Yeah, it can be counterintuitive to take the salt tablets, but sometimes necessary, even though it's against what maybe you were initially told. So this has been a really thorough discussion and overview, and I'm wondering as we close this podcast episode, what words of advice or encouragement do you have to the para pheo community?

Dr. Jaydira Del Rivero
Before I decided to do a second fellowship in oncology, you asked earlier why I wanted to do this, and it's because more than 10 years ago, we didn't have options. We didn't have any approved agent for pheochromocytomas and paragangliomas. But I have to say in the last decade or so, we have seen some advancements, not only for the other neuroendocrine tumors like in the pancreas, we have seen a lot, we have learned so much about pheo para, not only from the genetic perspective, but also from the imaging perspective. What kind of images we can do in those patients. What are the genes that has been discovered that has been associated with pheochromocytomas and paragangliomas that now help us to understand more about the biology of these tumors to then develop treatments. So initially, when I started seeing patients with neuroendocrine tumors for pheos and paras, there were not many treatments. Being a rare cancer sometimes this has been very difficult to do these studies. But now I have to say that I feel hopeful because we now understand more about the biology of these tumors. Now because of that, we are now able to develop therapies and [studies] for clinical trials. Like for example, belzutifan was recently approved for VHL (von Hippel- Lindau) related tumors and we feel that that can also be a good option for pheochromocytomas and paragangliomas. And there is an ongoing national study with belzutifan for these patients as well. I'm very fortunate as well that I'm the National co-chair together with Dr. Perez from Dana Farber for a treatment for pheochromocytomas and paragangliomas with another chemotherapy, oral chemotherapy called temozolomide, and it's a study that either patients receive temozolomide or they get temozolomide in combination with olaparib, because we feel that our hypothesis by adding olaparib, temozolomide can be more effective. And there are ongoing studies with a tyrosine kinase that I discussed earlier with axitinib, Dr. Fojo at Columbia University has a study. Or cabozantinib, Dr. Jimenez at MD Anderson has a study. I think that I have to say for our pheo para community, I'm feeling very hopeful. We're learning so much about this tumor type. I think there are ongoing treatment studies that can definitely help these tumors, not only shrink the tumors, but also destabilize this tumors for long term. I want my patients to feel hopeful because I know that we have better treatments, more treatments and that's because of you. That's because of the patients. We learn from the patients. I always tell my fellows, our patients are our best and where we learn the most. It's not all about books, or what we learn in books, our patients is how we learn the most. And by listening to our patients, we can understand more about disease, we can then develop guidelines for those patients. Of course awareness too. I think an increase of awareness of these tumors can definitely help us not only understand but also detect those tumors earlier. So I have to say I'm very hopeful. We're very excited here that we have, together with Dr. Karel Pacak, a pheochromocytomas and paragangliomas therapeutic programs with a natural history study that help us see patients long term but at the same time, treatment studies here at the NIH. So we are excited about that.

Lisa Yen
There are many reasons to hope, and thank you for being part of that reason because there wouldn't be this many advances and clinical trials and better understanding and awareness if it weren't for people like you who are so interested and dedicated to this field. So thank you for all you're doing for

the field of para pheo, for NET in general, for cancer and for all of us. From the bottom of their heart, thank you so much.

Dr. Jaydira Del Rivero
Thank you for having me here. Thank you and see you again soon.

Lindsey Jeu De Vine
Thanks for listening to the LACNETS podcast. We want to thank our podcast supporters Advanced Accelerator Applications, Tersera Therapeutics, and Ipsen Pharmaceutical. We also want to thank Progenics Pharmaceuticals, a Lantheus Company for making this special podcast episode possible. For more information about neuroendocrine cancer, go to www.LACNETS.org