You can find information about subscribing to this series at netrf.org/podcast, where you'll also find helpful charts, graphs, and videos that expand on this material.

If you're new to NETWise, we strongly recommend you go back and listen to the series from the beginning, starting with episode one. It will give you a solid grounding in the basics of neuroendocrine tumors and how they're treated. You can find the whole series 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 e-mail us and let us know! podcast@netrf.org

---

Welcome to NET Wise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. My name is Elyse Gellerman from the Neuroendocrine Tumor Research Foundation.

For our third exploration of NET primary sites, we're going to talk about the pancreas, one of the most common places for NETs to develop and a site with NETs that have a very distinctive set of characteristics.

Your pancreas is basically a giant gland shaped like a long squishy triangle. It's tucked up behind your stomach with one end connected to the place where your stomach meets the duodenum. That's the first section of the small intestine.

It's a delicate and complex organ with a crucial role to play in producing the important chemicals like hormones and enzymes that keep different parts of your body running and working in synchrony with each other.

The vast majority of pancreatic cancers are what are called "pancreatic adenocarcinomas", and they are some of the most aggressive and difficult to treat cancer. Pancreatic neuroendocrine tumors are much less common, but often much more treatable.

Here's Dr. Philip Philip from the Karmanos Cancer Center in Detroit:

> ***Philip:*** *"Although the pancreatic neuroendocrine tumors arise from the pancreas and so do the pancreatic adenocarcinoma, they're really very different diseases."*

Because pancreatic neuroendocrine tumors or PNETS are rare cancers and their behavior and treatment are so very different from other kinds of pancreatic tumors, it's really important that a careful diagnosis is made by a pathologist who has a lot of experience with this kind of cancer.

> ***Philip:*** *"An inexperienced pathologist may occasionally give the wrong diagnosis like confuse one with the other, so that's one of the reasons why we encourage always patients who've been diagnosed, for example, in a community setting where it's very rare for them to see those tumors,*

to have a second opinion, certainly in a more experienced center."

Careful diagnosis is particularly important with Pancreatic NETs because they can vary quite a lot from one individual's tumors to the next. While almost all PNETs are less aggressive than standard pancreatic adenocarcinomas, there is a wide spectrum of behavior among PNETS. Here's Dr. Emily Bergsland, Director of the Neuroendocrine Tumor Program at the University of California, San Francisco.

Bergsland: *"They really range in the biology and I think potentially more so than neuroendocrine tumors arising in other sites. I think we see a really wide range in variability of the behavior of the tumors from very, very slow growing to more rapidly growing.*

In the most indolent cases, some of our patients will have disease that has growth that's hard to measure over months and sometimes actually you need to look over a few years to see evidence of the tumor growing. And that's in distinction to tumors that are poorly differentiated neuroendocrine carcinomas. And in those cases, we sometimes see changes in tumor growth over a matter of a few weeks. So, there is this very big range in tumor growth, which can present a challenge when somebody is diagnosed."

The PNETs at the more slow-growing end of that spectrum can often develop for years or even decades before they are

discovered and diagnosed, so they are often discovered just by accident.

> ***Philip:*** *"For example, like you're doing a CAT scan for someone who has kidney stone or you're suspecting or anything which causes discomfort of the abdomen, pain, which requires a CAT scan, and then you find something tiny in the pancreas and then you look more carefully and you may do additional testing, and it turns out to be a neuroendocrine tumor."*

Because they so often go undiagnosed for a long time, pancreatic NETs have often metastasized outside of the pancreas before they are discovered and treated.

> ***Philip:*** *"More than 50% of the patients that come to us have developed a disease that has gone to other sites. And the common sites that they go to, the commonest will be the liver. It can go to the lining of the abdomen. We call it the peritoneum. It can also go to other sites like bone and at times go to the lungs.*
>
> *The metastases happen over many years, and I would say even sometimes decades in some patients. So, when a patient comes to us and they have what appears to be disease that has spread to other sites, we tell them that you have this disease going on for the last, you know, 15-20 years. And sometimes, it's hard for the patient to understand that or even accept that as a fact, but that's the reality. These*

tumors take a long time to develop and this spread happens over a long time."

An interesting feature of pancreatic NETs that hasn't often been observed in other kinds of neuroendocrine tumors is the ability to change their grade over time. Most NETs are either high grade (meaning fast growing and aggressive) or low grade (meaning slow growing and indolent), and they stay that way throughout the course of the disease, but some PNETs seem to become more aggressive as they grow.

Bergsland: *"Really, historically, we would do one biopsy at the time of diagnosis and we wouldn't necessarily ever do another biopsy again. But, over time, as we've now been better able to characterize these tumors – and I think many of us are doing more biopsies over time – what we're seeing is that there are some patients who have tumors who, over time, their Ki-67 will go up. What causes that change, we're not sure, but there are some patients really the tumors do shift into a different gear at some point later in the disease course. The term people have used for this is grade progression. I would say this is a fairly poorly understood phenomenon. We know it happens, but I would say we're not entirely sure in what fraction of patients this happens."*

No matter the grade, the first treatment for PNETs is often surgery. We talked in some detail about pancreas surgery

options in Episode 3 of this series where we learned there are basically three approaches – "enucleation", which removes just the tumor itself and leaves the surrounding pancreas intact; "distal pancreatectomy", which removes the 'tail' of the pancreas – the part that extends out under the stomach, often along with the spleen, which is next door, and any surrounding lymph nodes; and finally the more complicated "Whipple" procedure, which removes the 'head' of the pancreas along with the bile duct and parts of the stomach and small intestine that are connected to it.

And while surgery on the pancreas can be tricky because it's an especially soft and delicate organ, all of these procedures are performed often and successfully by surgeons who specialize in them. And in cases where the disease remains localized, surgery can be curative.

> ***Philip:*** *"If it's localized only to the pancreas, you will tell the patient, 'I am doing an operation. It's a bit of a major operation, but I'm trying to cure you off the cancer.' Yes."*

While catching a tumor early and cutting it out early is almost always the best way to avoid spread, because of the delicate nature of the pancreas, occasionally doctors will actually recommend waiting before performing surgery to allow the tumor to grow a bit, making it easier to remove.

> ***Philip:*** *"If the tumor is small, less than 2 cm, then I think there should be discussion of… you may even consider*

keeping it there and just watching it, and maybe removing it if it starts to grow maybe a bit faster or something like that happens. And if it's a very small tumor, like 1 cm or less, then there's a very good reason, today, just to leave it there for the time being. If it's 2 cm or larger, then the recommendation is to do the operation, for sure."

For PNETs that have metastasized to distant organs, surgery is also often considered, such as the liver debulking procedures we've discussed in previous episodes. While these are not curative, they can offer relief from symptoms and set the clock back on tumor growth, sometimes even by years.

Patient Story: *"My name is Joe Kennedy. I live in Maple Glen, Pennsylvania. I'm 58 years old. And last August 2019, I was diagnosed with pancreatic NETs.*

So, I had no inclination that anything was wrong and that the PNETs was brewing for most likely several years. I just had a strange pain in the abdomen area – just different… just an odd feeling.

So, instead of going to my primary doctor, it would have taken a day or two, my wife said, 'Why don't you just go to one of these urgent care facilities? You'll just be seen faster.' Actually, my own thoughts was 'Oh, maybe it was an ulcer or just some indigestion type of thing.' I wasn't expecting anything. So, I went to urgent care. Out of

being cautious, they wanted me to go get an ultrasound if I wanted to. It was sort of left up to me.

So, I went to the ultrasound. And after the technician was finished, something odd happened. She said, 'Hey, could you sit down for a second? We just wanna make sure we don't need to take any other pictures.' So, I thought that was a bit odd, but it still didn't bother me at all. And then a few minutes later, she came out and said, 'Now the radiologist has called your doctor.' And it wasn't my doctor. It was the doctor at urgent care. '…and read him the results. And they're waiting for you at urgent care.' And I said, 'Oh, my, this is something quite unusual.'

So, that sort of put me in a state of, you know, quite a bit of anxiety there. So, my progression was I went to my primary care and then they got a CAT scan. A day later or so, I'm getting the MRI and then it was then an hour of me having the MRI. Here comes the primary care physician again saying, 'It looks like you have a rare form of cancer known as neuroendocrine cancer.' I didn't know what that meant. 'It looks like there are at least a spot or two on your liver and your lymph nodes are enlarged, so it looks likely that it's metastasized to your liver.' So, that news sort of doubled me over. I remember just sort of kind of grabbing my knees a little bit. And I had been praying that it was something else and not that.

I was thinking as I went to that first appointment, 'They're going to put me on chemo. And can I go to work?'

And all these things. And the first thing I hear from the doctor is, 'We think you're a surgery candidate.' So, my feelings perked up a bit and basically it was a whirlwind. I did do surgery about 2-3 weeks later. So, they removed the tumor, the tail of the pancreas, nearby lymph nodes. They removed my spleen because that was involved and my gallbladder because, if I had to go on SSAs at some point in the future, they'd take your gallbladder out while they're in there because of gallstones.

I was in the hospital for a week. Little complications of heart rates being too high and all those kind of things. And then just recovering from abdominal surgery is a chore I'm sure for anybody that's gone through it. And that was about a 6-week recovery at home. And first coming out of that, I could barely walk down the edge of my driveway and each day was just a little bit more and walking… and there was all kinds of GI issues that had to resolve itself. Since I only have half pancreas now, prediabetic or on the edge of diabetes. We're trying to keep an eye on that. And cholesterol went up and things like that. I had been very good at all those things, but now dealing with maybe some fallout of not having a full pancreas, and we're still working through that.

But, generally speaking, before the operation, I felt pretty good. I felt like a 58-year-old, you know, decent in-shape person. I'm very lucky to feel the same way now because I was told, and as I fully understand, that this is not a question of 'will it return', but 'when will it

return.' And given that I already have it in the lymph nodes, then that even makes it more close to home, so it's definitely not curative. It goes into that, which I keep getting taught and keep understanding that it becomes a chronic condition. For right now, we're waiting and trying to keeping all the tools in the toolkit in order not to use them too early given my age at 58."

There are always complications that are possible after surgery, particularly major surgeries like a pancreas resection. In addition to the normal risks of infection, there are possible complications that are unique to pancreatic surgery.

Philip: *"They're not complications that will debilitate the patient in the long run, but they are complications that need to be addressed by a multimodality team usually between the medical oncologist, surgeon, and also a gastroenterologist. Add to that a nutritionist or a dietician."*

One of these is the occasional development of a leak known as a fistula.

Philip: *"So, a fistula formation – the leak – is because the pancreas itself releases digestive enzymes to break down the food in the lumen of the small bowel. However, the same digestive enzymes can also— If they're in touch with the wrong part of the anatomy, they can produce a digestion of the small tissue, the structure of the*

pancreas, which leads to a tract, if you would, that will lead to a connection between the duct of the pancreas and some other hollow areas. So, that's the pancreatic leak. And there's a percentage of patients who can get that, but it's not something which they will live with it forever because usually you'll be able to let it heal. There are different things you do to let it heal.

And if you're removing part of the pancreas, then you may end up with a lower rate or ability to secrete those digestive enzymes. And as a result, the patient might suffer from something called malabsorption, which means that fatty food are not really absorbed appropriately. It may lead to bloating, gas, loose bowel movements. We call them steatorrhea. Sometimes patients end up with weight loss. The treatment for that is to supplement the patient before they eat with tablets that are the enzymes that would have been released by the pancreas. Removing part of the pancreas may also put you at risk of worsening diabetes. If someone is predisposed to developing diabetes, it's simply because the pancreas produces the insulin that helps to control the blood sugar."

If you think about the fact that one of the primary functions of the pancreas is to produce hormones, it's not surprising that NETs that develop in the pancreas can cause hormonal symptoms. While functional small bowel NETs almost always produce serotonin, functional PNETs can produce a wide variety of different hormones.

Bergsland: *"First off, it's important to note that most tumors are what we call 'nonfunctional', which means that they don't make any hormones that cause a clinical syndrome. But a subgroup of pancreatic neuroendocrine tumors will make hormones in excess that cause symptoms in a patient. It's probably somewhere in the 10 to 30 percent range are functional. It can make a range of hormones, including glucagon, and insulin, and vasoactive intestinal peptide, and others.*

One would be gastrin excess. And when gastrin is overproduced, it will actually cause recurrent ulcer disease. So, patients might present, for example, with recurrent gastrointestinal bleeding from ulcers or abdominal pain, and also diarrhea can happen in that setting. And when gastrin excess happens, there are a couple of different approaches just to treat the hormones, but one that's very important is proton pump inhibitor therapy."

"Proton Pump Inhibitor" might sound like something you'd find on a spaceship, but it is actually just a particular kind of antacid.

Bergsland: *"We usually give it at double dose and that's a very important strategy to help protect from ulcer disease in that population, but we also will often use somatostatin analogs to help control the disease in addition to treatments that I use to treat the underlying tumor."*

Functional PNETs can also produce Insulin.

Bergsland: *"Insulin's normally made by the pancreas. But when it's an excess, it can really wreak havoc and patients will present with low blood sugars and confusion, sweating. And sometimes, in addition to these very acute symptoms, some patients just have a global loss of what we call 'executive function', where it's just harder for them to do just their normal activities. And the other problem with insulin excess is, over time, patients compensate for these low blood sugars by eating more and eating at strange hours, and so weight gain is actually also commonly seen in patients with insulinoma.*

But it's a kind of an example of… it's a normal role of the pancreas to make insulin, but it's normally well-controlled. And in the setting of a pancreatic neuroendocrine tumor, it doesn't have the tight regulation that it should have and it becomes a relatively urgent situation to fix, in that case.

Another hormone also produced normally by the pancreas, but can be produced in excess by pancreatic neuroendocrine tumors, is glucagon. And you see the opposite effect in that. That can actually cause diabetes and high blood sugars. And again, it's really inappropriate production of glucagon for that level of sugar. So, it's sort of the opposite type of tumor than an insulinoma.

And the last one we see with some… it's rare, but we also see… is vasoactive intestinal peptide excess."

In a healthy person, VIP has a role in controlling the amount of water and electrolytes released into the digestive system. An excess of its production causes digestive dysfunction that can really be quite debilitating.

Bergsland: *"That actually produces a really, really watery diarrhea, which can be very, very severe and can be associated with electrolyte abnormalities. Some people describe it as a cholera-type diarrhea… so, you know, like the infection cholera where it's just a very watery diarrhea where patients will often land in the hospital from dehydration and very low potassium levels. Luckily, it's very sensitive to somatostatin analogs, so we can use that as a bridge while we're trying to control the tumor.*

In all of these types of functional tumors, somatostatin analogs play an important role. But in each individual case, sometimes there are other drugs we use to manage the symptoms."

There are a number of systemic medical treatments available for PNETs. More than for many other kinds of NETs.

Philip: *"Pancreatic neuroendocrine tumors are generally speaking more sensitive or more responsive to what we call 'systemic treatments.' There's a drug called, for example,*

sunitinib or Sutent is the trade name. That drug works in patients with neuroendocrine tumors for the pancreas. It's approved for that. But at this time, it's not approved for patients with small bowel neuroendocrine tumors.

The other thing is that, in general, the conventional cytotoxic drugs or chemotherapy do not work well in small bowel neuroendocrine tumors or as they work better and sometimes much better in patients who have pancreatic neuroendocrine tumors. For example, I would use capecitabine and temozolomide. It's a 2-drug combination of cytotoxic drugs. I will use it in patients with pancreatic neuroendocrine tumors, but I will not use it in patients with small bowel neuroendocrine tumor, for example.

So, the range of the drugs that are available for pancreatic neuroendocrine tumors is a bit wider."

As in other neuroendocrine tumors, PRRT (peptide receptor radionuclide therapy) can be an effective treatment option that many hope will be made even more effective as it is further refined.

Philip: *"The question is, how much does it help? Is it more? Could be even more than what it does in small bowel tumors, keeping in mind that chemotherapy itself works better in pancreatic neuroendocrine tumors. And the second point is can we do even better by putting drugs on top of*

PRRT in pancreatic neuroendocrine tumors? So, this type of work is currently ongoing."

Bergsland: *"Prospective randomized data are lacking, and we actually don't completely know the response rate in that, you know, how many patients actually have shrinkage. We think a subgroup definitely does benefit in terms of shrinkage and almost certainly benefits in terms of disease stability over time, but we don't really know if everybody needs the same dose of radiation, if everybody needs four treatments, if there are other radiopeptides that might be as efficacious or more efficacious in some patients or all patients. These are all areas of research now. I think it's really great that PRRT is now part of our armamentarium, but I think there's more work to be done to try to refine that and figure out how to optimally use that in patients.*

And then, of course, I think we're interested at finding new drugs. And I would say in addition to novel radiopeptide conjugates that are in development, people are still trying to refine and look at the use of angiogenesis inhibitors. Sunitinib is already approved, but there are other drugs out there including surufatinib, which is a multi-targeted tyrosine kinase inhibitor that has activity in pancreatic neuroendocrine tumors. And there's an ongoing Phase 3 study right now called the CABINET study looking at a drug called cabozantinib, which is also sort of a second generation multi-targeted tyrosine kinase inhibitor in pancreatic tumors."

As with many kinds of NETs, the struggle with ongoing treatment is that there a lot of options for stabilizing a tumor – pausing or slowing its growth – but PRRT is one of the few actually has the potential to shrink tumors. Seeking new techniques and compounds that can go beyond stabilization is an important area of research.

> ***Bergsland:*** *"We live with stability because that's what a lot of our drugs like everolimus, sunitinib, and somatostatin analogs do, but ideally you'd see shrinkage. And particularly for people who have bulky disease that might be causing discomfort or disease that's causing hormone excess, those are situations, particularly if somatostatin analogues aren't controlling the hormones, where you really would like to have therapy that can shrink it, not just stabilize it."*

A sad truth about NETs is that we really don't know what causes the vast majority of them to begin developing in the body. But with some PNETs, we can trace their inception back to one of a couple of genetic syndromes that can make a person vulnerable to these types kinds of cancer.

> ***Bergsland:*** *"So, right now, this is an evolving area, but recent data in pancreatic neuroendocrine suggests that maybe 15% of patients with a neuroendocrine tumor of the pancreas have some sort of underlying hereditary syndrome. And what that means is it's a gene alteration that was*

present at birth in all cells of the body and actually can potentially be passed on to children. And that gene alteration leads to production of an abnormal protein in cells that can increase the risk of cancer. And it turns out there are several different syndromes that have been associated now with pancreatic neuroendocrine tumors. Probably the most common is multiple endocrine neoplasia type 1, also known as MEN1.

And these patients have a mutation in the MEN1 gene, and they most commonly present with hyperparathyroidism, which is a little benign tumor of the parathyroid gland, but it leads to high calcium levels, and that's a very common presentation for MEN1. And patients may have tumors of the pituitary gland as well as pancreatic neuroendocrine tumors and NETs of other sites. So, that's the most common one. And then there are other syndromes that have been associated with Pan-NETs including tuberous sclerosis, neurofibromatosis, and Von Hippel-Lindau syndrome.

And then, beyond that, a new syndrome was discovered not too long ago that looks a lot like MEN1, but this one's associated with a mutation in the CDKN1B gene, so a different gene, but a very similar result in terms of the hyperparathyroidism, pituitary adenomas as well as pancreatic neuroendocrine tumors.

And then finally, while infrequent, mutations in some other genes that can be inherited such as CHEK2, and BRCA2, and

MUTYH have been associated with pancreatic neuroendocrine tumors.

And then the last one is BRCA2, which is only rarely altered. Probably only 1% of pancreatic neuroendocrine tumor patients have a germline BRCA2 alteration, but we know that those patients, at least extrapolating from other tumor types like breast cancer or prostate cancer with BRCA2, there may be a role for certain types of chemotherapy as well as PARP inhibitors in that population. But again, data specifically for pancreatic neuroendocrine tumors are lacking right now."

It's often a good idea, especially for younger patients with pancreatic NETs, to be screened for these genetic conditions, first, because they can cause those other kinds of tumors, sometimes simultaneously with NETs and, second, so you can make your family members aware of a dangerous predisposition they may have.

These kinds of genetic predispositions arise from something called "germline mutations", genetic differences that are inborn and can be passed from parent to child. PNETs also have a higher likelihood than other NETs of "somatic mutations" – genetic alterations that develop in the tumor itself and are not present in rest of the patient's body. These are not yet well understood, but in the future, they may point to new treatment options for pancreatic NETs.

Philip: *And these somatic mutations sometimes can devise a better clue on whether they are a grade II or grade III or they are poorly differentiated, which is the very aggressive form of neuroendocrine tumors. They can sometimes even, maybe – hopefully soon – help us to decide which is the best treatment, so help us in personalized medicine using targeted drugs."*

Bergsland: *"And there are probably many other molecular alterations that exist that remain to be identified that may distinguish these patients with different types of tumor biology and different responses to therapy. So, I definitely think one big area of research is really in trying to figure out how to individualize therapy because, right now, we really have a wide range of treatment options, but we don't really know the optimal sequence of therapy in a given patient. Each strategy I think is really important, and I hope that that will become clearer over time. I should note there are studies out there that are looking.*

So, for example, the COMPETE study is looking at PRRT versus everolimus in somatostatin refractory GI and pancreas NETs. And there's another study that's in development that potentially will be looking at PRRT versus chemotherapy. And I think it's really just trying to get at how do we know what sequence to use in these patients."

As we have talked about in this episode, PNETs present lots of challenges in the laboratory and the clinic. They differ from person to person and sometimes even over time in how quickly they grow and spread, whether they produce troublesome hormones and symptoms, and whether they respond to specific treatments. But there are a lot of treatment options for PNET patients. And it's good to know that there are scientists and physicians around the world working to answer the questions that remain so more and better treatments can be developed and tested. More knowledge about PNETs makes it possible to personalize treatment. So, if you're living with PNETs, please talk to your NET physician about your options for the best possible outcomes.

Thanks for listening to NETWise. My name is Elyse Gellerman, and I'm the CEO of the NET Research Foundation. This episode was produced by David Hoffman of CitizenRacecar, assisted by Garrett Tiedemann. It was made possible by the generous support of Ipsen, the Vincent E. Taylor Patient Education Fund, Advanced Accelerator Applications (a Novartis Company), and Lexicon Pharmaceuticals. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. This is a production of the Neuroendocrine Tumor Research Foundation where we're committed to improving the lives of patients, families, and caregivers affected by neuroendocrine cancer by funding research to discover cures and more effective treatments and providing information and educational resources. Please visit us at netrf.org.

This podcast is not intended as, and shall not be relied upon as, medical advice. The Neuroendocrine Tumor Research Foundation encourages all listeners to discuss any scientific information found here with their personal oncologist, physician, and/or appropriate qualified health professional. Listening to this podcast does not constitute a patient-physician relationship. The Neuroendocrine Tumor Research Foundation does not represent that any information provided here should supplant the reasoned, informed advice of a patient's personal oncologist, physician, or appropriate qualified health professional.