NETWise
A Podcast About Neuroendocrine Cancer

Episode 2: Imaging, Testing, and Building a Care Team

Transcript

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

As we talked about in the last episode, diagnosing NETs is really tricky. It can involve many doctors doing multiple tests to rule out more common diseases. This can be a frustrating process, but unfortunately, it's necessary.

Here's **Dr. Mark Lewis**, Director of Gastrointestinal Oncology at Intermountain Healthcare, a system of hospitals in Utah and Idaho:

> **Lewis:** *"Primary care in particular is difficult. It gets grossly underrated. It's not as glamorous as neurosurgery. But primary care doctors are the first line of defense for patients. This is how I've heard their job described. Imagine you're standing by a train track and you're watching a train go by and you're looking at faces at the window, and it's all a blur and you have to pick out the one person who's sick. That to me is a perfect analogy for the NET patient. You may see 30 cases of irritable bowel syndrome, and one of those people actually has carcinoid syndrome and you got to pick them out.*
>
> *So a lot of NET patients have had the experience of misdiagnosis or delayed diagnosis."*

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This episode is all about information. How do your doctors gather the information they need to correctly diagnose your tumor and recommend the right course of treatment?

NETs are complex. There are multiple options for diagnostics and surveillance. On a basic level, your doctors are trying to describe your tumor in a way that other doctors and members of your care team can understand. This description includes some elements we talked about last time – Where is your cancer? What is its "stage", meaning has it metastasized? Then we're going to add new descriptors – first, your tumor's "grade", and is it "well-" or "poorly-differentiated". More about those in a moment, but first, lets talk about all the ways your doctors will gather the information they need to make these assessments.

It almost always begins with imaging – taking pictures of the inside of your body to find the tumors and begin to learn about them and how they behave. This can be done in several ways. Some kinds of imaging, like X-rays, CAT scans, and MRIs, they're "anatomical", meaning they allow the doctors to see the shape and structure of a particular part of the body; and some are functional, meaning they show something about chemical reactions happening inside cells.

Here's **Dr. Richard Wahl**, head of the Department of Radiology at Washington University School of Medicine in St. Louis.

> **Wahl:** *"As radiologists and clinicians, we have a bunch of ways to look for tumors in the body. We have options of looking anatomically, that is like is there a mass or not, or functionally, or sort of a hybrid of both."*

The first step for most doctors who are trying to diagnose something they think may be a NET is often an anatomical scan called a CAT or CT scan, which stand for Computerized Tomography. CT scans are basically X-rays, but rather than a single flat image, the machine takes multiple X-rays from different

angles. Those images are then assembled by a computer into a three-dimensional picture.

Here's **Dr. Pamela Kunz**, Director of the Neuroendocrine Tumor Program at Stanford University, followed by **Dr. Rathan Subramaniam**, Professor of Radiology and Chief of Nuclear Medicine at University of Texas, Southwestern Medical Center in Dallas:

> **Kunz:** *"So, a CT scan a patient will lay on an exam table with a sort of tube around them and pictures are taken using X-rays, and those pictures are then put together that provide a three-dimensional view of the body. And it's often done of the area they're pointing to, you know, 'it hurts here'."*

> **Subramaniam:** *"It's similar to like the slices in a loaf of bread. So it takes images almost like slices through the human body, and allows us to see almost every part of the human body, including bones, blood vessels and all the inner organs inside. And it can go from head to toe, and it's a very quick examination in the sense that it can be done from head to toe within a few minutes."*

Another kind of scan is called an MRI, that's short for "Magnetic Resonance Imaging". These use magnetic fields instead of radiation.

> **Subramaniam:** *"It's a totally different kind of imaging test. It's a technique that uses magnetic fields and radio waves to create detailed images of the organs and tissues within the human body"*

> **Kunz:** *"They're both usually done with a form of contrast, which means that a patient will get an I.V. line, and then a medication infused through that I.V. line, and that contrast goes through the blood vessels and helps enhance different features of the body, depending on what contrast is used."*

These two scans use different technologies, so they see different things, and there are kinds of NETs that will show up clearly on a CT but not be seen at all on an MRI and vice-versa.

Here's **Dr. Sumeet Virmani**, a Radiologist at Rush University Medical Center in Chicago:

> **Virmani:** *"It really depends on the tumor location. If the patient has a pancreatic tumor, this is well delineated on the MR. If the patient has a hepatic tumor, it can be seen on both MR and CT. If a patient has a small bowel tumor, it will not be picked up on the MR, so each modality has its positives and negatives."*

As we mentioned, there's also an entirely different kind of imaging that radiologists can do - functional imaging. Instead of looking at the physical structure of a part of the body, they make pictures of the internal activity of cells. The commonly used kind of functional scan is called a PET, or Positron Emissions Tomography, scan. When functional scans are combined with anatomical scans, a hybrid image can be built that gives a rich view of both tumor activity and location. This is called a "PET/CT", Positive Emission Tomography and Computer Tomography.

> **Subramaniam:** *"A PET/CT scan, when we say PET/CT scan, it combines these two different modalities, a PET scan as well as a CT scan. What it does is it gives us much more clarity where this chemical reaction is taking place. So when we look at those scans, we can pinpoint exactly which part of the body it's taking place. That's why the CT scan combined with the PET scan is a really valuable test."*

To find and scan activity in tumor cells, a radio tracer is used. These work because particular kinds of cells have an affinity for some chemicals, attracting them and processing them. This is referred to as the cells having receptors, or expressing receptors, for that chemical.

> **Subramaniam:** *"There are different types of tumor cells that express different type of receptors or antigens on their cell surface. And they are intrinsic to those tumors."*

Now, if you take some of that chemical and attach it to a small amount of radioactive material, you've made a radio tracer. Then, when you release that

compound into the bloodstream, it will seek out the cells that have those particular receptors. Then on the scan, the cells that express those receptors literally light up.

> **Subramaniam:** *"It shows the higher levels of chemical activity. That's what it is, and t hese areas show up as bright spots in the scan."*

You may have heard of an FDG PET/CT scan. This scan shows how active tumor cells are using a radio tracer called "18F fluorodeoxyglucose". This can be an effective scan for some cancers. Activity can be measured by understanding how fast tumor cells use up a sugar called glucose. More active tumor cells use more glucose and light up brighter on the scan. The catch is that slow growing NETs, they're just less active than other cancers, and they may not light up brightly, or not at all.

Luckily, there are other options for NETs using a different radio tracer. Many neuroendocrine tumors do express receptors or hormones called somatostatin. Somatostatin is a growth hormone that helps you control the endocrine system.

Here's **Dr. Ed Wolin**, an oncologist who is Director of the Center for Carcinoid and Neuroendocrine Tumors at Mt. Sinai Medical Center in New York City:

> **Wolin:** *"Somatostatin is a natural hormone in the body, it binds to a somatostatin receptor which is on the membrane of certain cells. Eighty to ninety percent of neuroendocrine tumors have somatostatin receptors. Natural somatostatin binds very well to the receptor, and so does its analogues, and then after binding to the receptor it internalizes inside the cell and gets stuck inside the cell, where it exerts its actions."*

This is especially useful because very few other cells except neuroendocrine tumors have this characteristic. So if we release artificial somatostatin — called a "somatostatin analogue" — into the blood stream, it will seek out any NETs that are in the body and stick to them. As we'll hear in a later episode, this is the basis for several kinds of useful treatments for NETS. It's also behind a new kind of imaging, which has only been available for use

in the United States since 2016 – something called a "Gallium-68 Dotate PET/CT".

> **Kunz:** *"When patients go in for this newer scan, they get an injection of a material with a protein called octreotide and a very low dose of radiation called Gallium 68. And the Gallium 68 serves as a lightbulb, so that when it's infused, the Gallium 68 and the octreotide attach to that somatostatin receptor like a lock in a key – so it's a very specific relationship. And so, in doing so, when the Gallium 68 attaches to the cancer cell, and we take a picture, it lights up like a lightbulb where the cancer cells are in the body."*

You may also heard of an scan called "Octreascan", which has been available in the United States since the early 1990s. The Octreascan uses a similar mechanism to light up neuroendocrine tumor cells using somatostatin, but it uses a different radio tracer than the Dotate Gallium scan, and there are major differences between the two.

> **Virmani:** *"So, octreotide scan has been there since 1994, it was approved by (the) FDA in 1994, and we were very happy with that, we were able to see a lot of lesions, but when Gallium 68 Dotate PET/CT came, it proved that we were all wrong, and there were a lot of lesions we were missing on octreotide. It's a quicker scan, it takes about two hours, as compared to the Octoscan (sic) which usually takes about two to three days. It has better images. It is very highly sensitive – the images are very clear, crisp, high-resolution."*

And in just the few years since Gallium scans have become available in the U.S., they have already become essential to the way NETs are diagnosed and treated. They are particularly useful because they can help find tumors that might otherwise be missed.

Here's **Caroline Creamer**, a Physician Assistant who works with NET patients at the University of Pennsylvania Medical Center:

> **Creamer:** *"The Gallium scans are really important with an initial diagnosis, because it gives us a good idea of where the primary is and if there is any spread of disease, and if so, where that spread is. It*

helps determine if they're a surgical candidate, or if, you know, we can target their disease with liver-directed therapies, and basically how we can kind of target treatment."

Gallium scans can also be extremely useful for finding the extent of metastasis, which is invaluable for doing things like planning surgery.

Here's **Dr. George Fisher**, who specializes in treating NET patients at Stanford University Medical Center:

Fisher: *"If a surgeon was going to go in and do a big liver surgery, but in fact found spots elsewhere that were concerning, the surgeon might think twice about doing a big liver surgery if he knows that there's going to be disease outside the liver that would be neglected. Or, the surgeon might say, "well, I can go get that, too". So if the Gallium dodatate scan found a spot on the tail of the pancreas, the surgeon says, "no problem, I'll go ahead and take out the spots in the liver that I can see in that scan, and I'll take out the spot in the pancreas that I might otherwise not have seen."*

As exciting as this new technology is, it isn't perfect, for radiologists in the United States, they have only been looking at these for a couple of years, and they can be tricky to read.

Here's **Bonnie Bennett**, the Nurse Coordinator for the NET Treatment Program at Penn:

Bennett: *"It's a newer technology here in the United States, and our radiologists are getting used to reading it. And oftentimes at tumor board, we will look at the scan together with our radiologists – there may be something that's lighting up, but they're saying "no, that's just interference, or that's just physiologic activity". That's one thing that I think people don't understand when they read it on their report. It says there's physiologic activity in the thyroid and the liver and all these different organs, and they think, "oh my, I have tumor everywhere", but it's just the radiotracer going normally through the tissues that's being picked up; but it isn't avid, it isn't being picked up so that it glows brightly and it's an actual tumor site."*

Second, and more importantly, some NETs do not have somatostatin receptors. And those NETS, they do not light up on the scan.

> **Wahl:** *"Even in an individual patient, you can have instances where let's say the majority of the lesions are receptor-positive, and then there's a minority that are somatostatin-receptor-negative. So increasingly, we are what we call metabolically or functionally phenotyping these lesions using our scans to figure out are they all somatostatin-receptor-positive or is there a subset that's not positive for the receptor, but that are, in fact, there and alive, that we're going to miss if we give a targeted therapy?"*

Another way doctors might take pictures of your tumor that they can stud is with actual photographs or video recordings, using a technique called endoscopy.

Here's **Dr. Heloisa Soares**, Head of the Neuroendocrine Tumor Program at the University of New Mexico in Albuquerque.

> **Soares:** *"So when the patient is going for endoscopy, he will meet with the physician that provides that, such as a gastroenterologist, or sometimes our surgeon can do as well. They will receive some anesthesia to sedate them a little bit. Typically, it's not general anesthesia, it's just something to sedate the patients. They will then be laying on a table, and a camera will be introduced either through their mouth or through their anus and look for disease which could be for a tumor or for inflammation if the reason for that procedure is a little bit different."*

This procedure is particularly useful for gathering information about NETs in the Lungs, which can be accessed easily via the mouth and throat, and NETs in the rectum and large intestine, which can be accessed through the anus. It's much less useful for mid-gut NETs, like in the in small intestine or pancreas, because they're harder to get to. Endoscopy is not nearly as

invasive as surgery, but it's more involved than a scan, and so it requires a little more preparation on the part of the patient.

> **Soares:** *"That is an outpatient procedure, but the patients need to come fasting. Then often, especially if they're doing a colonoscopy, which is to look again in the colon and the rectal, they have to have some preparation to have the bowel clean so there's not stools. Because if you have stools when you're going with the camera, then you can miss a tumor. If you have your stomach full of food when you're going for an upper endoscopy, for example, it's not good, right, because the food will also potentially mask a tumor in addition to putting you at risk of aspiration, which is not good."*

Using biochemical tests, such as lab tests with blood and urine can be a bit tricky. They're not as useful for diagnosing NETs as scans or biopsies, but they can be helpful for monitoring disease progression.

A 5-HIAA test measures the amount of serotonin in the blood. Elevated levels of serotonin can be associated with a NET that is called "Carcinoid Syndrome". To perform this test, urine is collected in a container over a 24-hour time period.

> **Fisher:** *"You decide, well, I'm going to just ask for this 24-hour urine collection, and see if there's an elevated marker called 5HIAA, which is a metabolite of serotonin, and if the serotonin is causing the flushing and/or the diarrhea, I might find a high level of 24-hour 5HIAA in the urine collection. Then I can say, well, if that's high, I think that this is probably a carcinoid syndrome", and I'll go ahead and do the workup to look for a carcinoid tumor."*

To avoid inaccurate results, certain foods and over-the-counter medicines should be avoided for three-to-seven days before the 24-hour test.

> **Soares:** *"Because there are some medications and some foods that can potentially increase a little bit the levels in the urine, you should restrict yourself to a specific diet for that."*

Some foods to avoid include bananas, avocados, plums, eggplants, tomatoes, plantains, pineapples, and walnuts and cashews. Also avoid tea, coffee and alcohol. Over-the-counter medicines you should avoid include cough medicines, Tylenol and aspirin.

A Chromogranin A test is a blood test measuring CGA, a protein found in neuroendocrine tumors.

> **Soares:** *"I think the most common one, and the one the patient asks the most and finished the most, is called chromogranin A. You measure that in the blood. It's a peptide that in neuroendocrine tumor cells, they secrete and then it circulates in the blood. And then, there are studies that show it could be associated with amount of disease that the patient has, and also some coloration with survival. The caveat is that the sensitively and the specificity of the test is very variable. What specificity is that? If I have the test, does that really mean that I have the disease? Not necessarily, because there is a lot of false positives, meaning that there are other conditions that can increase your chromogranin level not necessarily related to endocrine tumors. Now, renal disease - someone that has a bad kidney - that can increase your chromogranin A levels, and someone that has bad heart disease. Also, if you are taking what's called PPI, or proton pump inhibitors, because you have heartburn, that can also increase your levels of chromogranin A."*

> **Fisher:** *"People in the community might have, you know, have one episode of flushing, or two episodes of loose stool, and their doctor may have exquisite awareness of neuroendocrine tumors or carcinoid, and will go ahead and get a chromogranin A and be sky high. And then, they refer him to me, because they think they have a carcinoid tumor. In fact, most patients don't have a carcinoid tumor, because they may have been taking some antacids, some pill to help decrease secretion of acid in their stomach, and as a consequence of that, they have a markedly elevated chromogranin A that has nothing to do with a tumor."*

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"My name is Samuel Prentice, Jr.

Basically, what happened was in 2002 I had a blockage in my small intestine. And up until that time, I had never had any health issues. At that time, I was 57 or something like that, I believe, and had never had any health issues at all. And what happened was, I developed a 72-hour case of the hiccups.

Basically, I went out for dinner on Friday night, woke up on Saturday morning with the hiccups, continued all through the day, went to urgent care. They gave me kind of like a hiccup suppression type of thing, and that seemed to help a little bit. But then Sunday they started in again, and so I ended up back in the hospital on Sunday. That's when they put a gastrointestinal tube down me and everything, and then started doing their diagnosis and their tests and so on and said that there was a blockage.

So I ended up in the hospital and having to have surgery, and they removed a two-inch tumor from my small intestine that they told me was cancerous. There wasn't any other evidence of cancer at all, so they just took out that two inches of my small intestine and sew me back up and said, "It's important to follow up with oncologists and everything in terms of getting ongoing tests." And so that's what I did. I think it was two months later I had another blood test and urine test. That continued on basically for the following year. About every two or three months, I would have this blood and urine test, and so on. Then it went to like four months and then six months.

Then they finally, after about three years, they did another CT scan, and they said they didn't find anything, so I could just go ahead and just have a yearly physical and include the urine test and the blood test with that, and then I'd have annual checkup and everything. Again, the blood test and urine test came back fine. There didn't seem to be any problem whatsoever.

Nobody had ever mentioned to me that that it was a neuroendocrine tumor. I had never heard of the term NET or carcinoid.

Then 2017, so 15 years later, what happened was I ended up having to go to the hospital because I was having significant gastrointestinal distress, lots and lots of pain and bloating and that sort of thing. It's something that I had not had. What happened then was that I ended up going in and having the surgery, and there was just this myriad of scar tissue all around my GI tract. And so they had to take out nine feet of my small intestine, including my ileum, and the connection with my colon and my appendix. That was the bad news. I had five-hour surgery with all this plumbing removed.

The good news was, if you can call it good news, was that they discovered that there was carcinoid cancer there. Because the test results are not indicated, that the blood and the urine test had not indicated that, so I didn't know that I had it, and, in fact, that it had kind of spread through my GI tract and metastasized to my liver. And the reason why it was so providential from my standpoint is that when they went in, not only did they discover that there was scar tissue thereabout, but that actually there had been a puncturing of my small intestine and I was starting to become septic. If I had waited another 24 to 48 hours, if I said, "Well, I'll wait and kind of tough this out," or something like that and so on, I would have died.

My life started revolving around healthcare appointments. It just revolves around appointments to the different specialists, oncologist, and GI doctor, and, of course, in the aftermath of my surgery, the surgeon, dietitian, physical occupational therapist, blood draw…

Then tests, I mean, there's been all sorts of scans, CT scans, MRIs, echograms - just lots and lots of tests. Your life starts to revolve around what is going on this week as far as some sort of test, or doctor's appointment, or physical therapy or whatever, and so on and so forth."

The next step is almost always a biopsy. A biopsy is a procedure that removes a small sample of tissue or fluid. This sample might be obtained by means of an endoscope, or by using a long needle, or sometimes by surgery.

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Kunz: *"Biopsies, when they're not done surgically, are usually done by an interventional radiologist who uses a needle with a small core. For example, let's say we're doing a liver biopsy, because someone may have cancer spots in the liver. Their skin would get numbed up. The interventional radiologists use a scan, either an ultrasound or a CT scan, to help guide where they're putting the needle, so that that needle goes into exactly where they want it. They take some samples of that, and then that gets sent to the pathologist.*

It is cut into very, very thin slices and placed on a slide. Then the pathologists can look at that under the microscope. And they will look at, number one, what do the cells look like? Number two, they do a whole series of special stains that help identify maybe where did it come from? What type of cancer is it? We rely very heavily on our pathologists"

A pathologist examines the biopsy sample to make a diagnosis, and to the expert eye of a pathologist, a NET looks very distinctive — quite different from both the healthy cells that surround it and from other tumors.

Here's **Dr. Aatur Singhi**, a Pathologist at the University of Pittsburgh Medical Center in Pennsylvania:

Singhi: *"Typically, the healthy cells within the small intestines or the pancreas, they're ordered, but they're small. They're inconspicuous. As opposed to the neuroendocrine neoplasm which just expands, and it continues to grow. But it's a very well-encapsulated, very circumferential neoplasm. It's not ill-defined. It's very distinct. And then, as you look at closer power, you start seeing the nuclei. The nuclei are extremely distinct when it comes to neuroendocrine neoplasm. They have what we call a salt and pepper chromatin appearance. And so, when you mix salt and pepper, they have a very kind of coarse architecture, where you see larger bits of pepper amongst little fragments of salt. It's very distinct. As opposed to, let's say, an adenocarcinoma or squamous cell carcinoma, or melanoma where the nuclei are very prominent - pleomorphic, big, gigantic, very mitotically active. In contrast, a neuroendocrine neoplasm is typically*

very inconspicuous, uniform. They don't hardly grow very fast. I mean, they're very slow growing neoplasms."

In addition to confirming that we are, in fact, dealing with a neuroendocrine tumor, pathologists can also make the determination about the differentiation and grade of tumor cells, which is crucial information for your doctors to decide what's next.

Differentiation, as it sounds, has to do with how alike or different the cancer cells are from the healthy cells around them. You see, any new cell, when it first divides, it begins as what's called a "stem cell", a cell that has the potential to become a part of any kind of tissue. The cell then "differentiates" to fulfill a particular function, becoming part of your skin, or blood, or lungs, or whatever is required.

Fisher: *"So that gets back to embryology, and cancer is where embryology goes wrong. When you start with stem cells, which the ultimate is the embryo from the egg and sperm, that's an undifferentiated state. As cells mature, they have to become functional components of some organ."*

Cancer cells sometimes successfully differentiate, looking and functioning somewhat like the surrounding tissue. And sometimes they don't, looking like something else entirely.

Fisher: *"So when you look at a sample of tumor under the microscope — any tumor, any kind of cancer — those cells may or may not try to emulate the tissue of origin. So, if you… I'm going to use other examples that people might have a better sense of… if you had… I think that most people know that breast tissue is glandular — it's glandular because it makes milk — and so if you have a breast cancer, it can look like glands. And if you have a tumor that still has architectural elements of glandular architecture, with cells that are fairly homogeneous in appearance, that might be a well-differentiated breast cancer, meaning that the tumor cells themselves are trying to emulate the tissue of origin.*

On the other extreme, we have poorly-differentiated cancers, and those cancers no longer look like, or even attempt to look like, the tissue of origin. Poorly-differentiated tumors have cells that are sort of erratic, they're completely a broad spectrum of sizes and nuclear shapes, they're not bearing any close relationship one to another, so they're not forming any distinct architectural pattern, they're just growing like sheets of cells in a very chaotic background."

Here's **Dr. Thor Halfdanarson**, an oncologist at the Mayo clinic in Minnesota:

Halfdanarson: *"Tumor differentiation has more to do about how the tumor cells look — do they look quiet and well-behaved, or do they look ANGRY? So the pathologist, an experienced pathologist, can look at this - just look at the slides - and tell immediately if this is an aggressively behaving tumor or not."*

Fisher: *"Now, the reason why the terms 'well-differentiated' and 'poorly-differentiated' are so important clinically, is because the poorly-differentiated tumors grow faster, are much more aggressive; they spread early and often. The well-differentiated tumors tend to grow slower, they tend not to spread as fast. And so, when I talk about this with patients, I think of well-differentiated as well-behaved, poorly-differentiated as poorly behaved, and they're less likely to respond to normal growth controls."*

Another key piece of data is a tumor's "grade", which is a measurement of how fast its cells are reproducing.

Kunz: *"So the the grade refers to how fast-dividing are the cells. There are three grades, primarily — grade 1, grade 2, and grade 3. And these are based on a couple of features, one is the KI-67, and the other is the mitotic index. They are both reflections of how fast-dividing these cells are. Slowly dividing is good, and fast dividing is bad.*

So, the KI-67 is a special stain. It's a protein stain that the pathologists apply to all of the cells that they are looking at, and the slower-dividing cells pick up this stain less frequently, and the faster-dividing cells pick up this stain more quickly. Or, more frequently, I should say. So when you're looking at…think if you're looking at a picture with a bunch of dots — the protein will show as a dot. There will just be a few dots for a grade 1. And that is a…The KI-67 is graded on a scale of 1 to 100, so that's 0 to 2; a grade 2 neuroendocrine tumor will have a KI-67 of 2 to 20, so there will be an intermediate number of dots; and then a grade 3 neuroendocrine carcinoma has a KI-67 of greater than 20, up to 100; and so that will have many dots that you see when you're looking at that stain on a pathology slide.

The mitotic index, however, actually does look at mitoses — which is the act of cell division. "

Singhi: *"You have this condensed chromatin which represents almost like tangles of string, and that's what a mitotic figure is. The pathologist counts the number of mitotic figures within a specific area, specifically two millimeter squared."*

Kunz: *"So that is also defined on a very similar scales to the KI-67, so zero to two, three to twenty, and then greater than twenty. So they are similar and complementary markers, but on slightly different scales, but we use both of them together."*

This grading system is used for all NETs, except those that start in the lungs, which have their own, slightly different system.

Wolin: *"With respect to lung carcinoids, pathologists have never been able to agree on what a KI-67 cutoff should be for different grades — they all fight with each other: should it be 5%? Should it be 10%? What are the limits? Nobody knows. So, the pathologists, to this day, are using the WHO classification system, which was developed in about 2010. They are divided, instead of grade 1, grade 2, grade 3, like we do for the intestinal ones, we talk about 'typical carcinoid', 'atypical carcinoid', and 'high-grade neuroendocrine tumors'."*

Grade has a lot to do with how NETs are treated and with overall prognosis — with grade 3, or high-grade, NETs being very different than lower-grade NETs.

> **Kunz:** *"Grade 1 and 2 tend to have a better prognosis, on the order of many years. The very aggressive, fast-growing grade 3 tumors could have a prognosis of months to a year or so, so very different than the grade 1 and 2 tumors."*

But please keep in mind that within these grades — particularly within grade 3 — there's a wide range of situations.

> **Wolin:** *"Grade 3 is a mixed bag. If somebody has 25%, 30%, 40% of the cells dividing, that's a different disease than if 95% of the cells dividing. Treatments are completely different."*

The grade of your tumor is not the whole story — it's one piece in a wide tapestry of information, gathered from different kinds of tests and imaging. You and your doctors will use all this information to make decisions about how to most effectively deal with your tumor. No one test or one scan will give you the whole picture of what's happening. NETs are complex, no two are alike, and even within that one tumor there can be a range of aggressiveness between the different cells.

> **Wolin:** *"You should use your head. If you have a tumor, and the doctor tells you it's grade one on a biopsy, written by a good pathologist, and he says grade one, and the cancer has doubled in size in three months, that's not grade 1! That's a cancer which is growing pretty fast! The reason that we see this type of thing is that a biopsy is just a little speck. If you do an endoscopic ultrasound of a pancreas and do a fine needle aspiration, and you say 'now I have a diagnosis of a pancreatic neuroendocrine tumor', OK, that's being based on a few cells you suck into a needle. Meanwhile, there's a whole tumor mass. Some areas in that mass might be actually pretty high grade and you might not even know it. So you have to use your head."*

The bottom line is that to understand your NET and treat it properly. You really need to get a range of viewpoints and opinions from doctors who are trained to look at your disease from different angles and using different diagnostic techniques.

> **Kunz:** *"Cancer care is, by definition, very multidisciplinary. Often patients need a surgery, and chemotherapy, and radiation or other procedures. I would say that NET care in particular really requires many disciplines involved. You can imagine also if someone also has hormone secretion, they need an endocrinologist — it really requires bringing all of those folks together."*

Here's **Dr. Eric Nakakura**, a surgeon at the University of California, San Francisco:

> **Nakakura:** *"So I think the core group is going to be surgeons, if surgery is in play; medical oncologists, if any kind of systemic therapy is in play; the radiologists who can help with characterization of diagnosis; the pathologists, who are critical to confirming the diagnosis, in some neuroendocrine tumors this can be very critical in getting the diagnosis right. Also, nuclear medicine physicians play a key role with new therapies such as peptide receptor radiotherapy, and also with PET or functional imaging. Interventional radiologists play a key role in what's called liver-directed therapy for patients with liver disease. So, I think those are your core group that you'd want to have, but there's also nutritionists who are very important, especially for patients with carcinoid syndrome, helping to control their diarrhea, or avoiding foods that can make the symptoms worse; symptom management, especially for patients with issues with pain, diarrhea, weight loss, things like that."*

Because NETs are different from other kinds of cancer, it's critically important that you get yourself seen by doctors who particularly specialize in treating NET patients. On the website for this episode, we'll post a list of hospitals around the country where you can be seen by some of the world's most experienced specialists in treating neuroendocrine tumors, maybe even some of the same doctors you've heard speak on this series.

At specialty NET treatment centers, sometimes your case will be discussed and reviewed by what's called a "tumor board", a multidisciplinary group who work together to present you with a plan of action for combatting your particular cancer, with all of its specific characteristics:

> **Kunz:** *"So a tumor board is really a panel of experts from different disciplines. So in our case we have a pathologist, who lets us see the slides under the microscope, which is actually really great. We have a radiologist who will review the CT scans or the MRIs. We have a nuclear medicine physician who re-review those gallium doda-PETs. We have medical oncologists, surgeons, interventional radiologists — so all in one room, and we will present the case of the patient. And that really helps us, specifically if there's a question, but I think that it's pretty good, routinely, to discuss patients in this forum. I always learn something, and I think it ensures that the patient is really getting multiple opinions to help determine the next best step."*

We strongly encourage you to visit and work with a knowledgeable and experienced NET doctor, even if you live far away, because after an initial set of consultations, they may even be able to collaborate with your local medical center to give you the best care possible.

> **Kunz:** *"Many patients live far, far away from NET expert centers, so I would say that the majority of patients who come see me live a many-hour drive away. So we often work with their local community oncologists and partner with them to implement the plan. I tell patients that I think that's really the best of both worlds — if they come to us for scans and regular input to get… input at times of key decisions, and they get the care implemented closer to home."*

And when you are working with an experienced team of NET doctors, it's important that you come prepared, taking a little time to work with your current oncologist or primary care doctor to assemble as much information as you can about what you've already done and who you've already seen.

> **Creamer:** *"So, the really big thing is making sure that all the tests that have been done since diagnosis are brought to the visit. That sounds like a very daunting task for someone that's just been*

diagnosed, because they probably can't even remember all the tests that they've had because it's usually such a whirlwind process. But the big thing – the really big things, would be any pathology reports - if they've had biopsies or if they've had surgery already - making sure those al make it to the appointment….any imaging that's been done – we usually request the discs of the imaging, so we can take a look at it ourselves and have our radiologist take a look, if we feel it's necessary, as well as the reports; and then any, whoever – if they're being sent to us by an oncologist, or whoever discovered this diagnosis – any notes from them, because it's someone who's probably been seeing them for a long time, and maybe they've had symptoms for years but they couldn't quite figure out why, and it's important for us to know how long those symptoms have been going on. And then any lab tests that have been done, of course we want those as well, we also don't want double up on anything that's already been done, in addition to as getting base knowledge of their case."

"My name is Mark Lewis, I'm a medical oncologist.

I'm the Director of Gastrointestinal Oncology at Intermountain Healthcare, which is a healthcare system based in Utah.

I got involved with the Neuroendocrine Tumor Research Foundation and the Board in the most selfish way imaginable, which is that I have neuroendocrine tumors myself.

As I was into my medical training, I developed abdominal pain. Doctors probably shouldn't diagnose themselves. I thought I had appendicitis. I didn't. I was even able to convince myself that some of my symptoms were due to other things, stress. Being a doctor, I thought that's why I was exhausted.

It turns out I actually had tumors growing in my body. I had high calcium, and that clicked for me because my father had had high calcium as well, and his doctors had told him it was he was consuming too much dairy. It turns out that was a clue that was missed.

And so, our family curse, if you will, is multiple endocrine neoplasia type 1. That's an autosomal dominant disorder. It runs through generations with a 50/50 inheritance pattern. For instance, I have two children. The way the coin flipped, one of them has MEN1 and one of them doesn't.

So I'm here and involved in NETRF both because I'm affected, but more importantly for me, because I'm the parent of a child affected with neuroendocrine tumors. I'm deeply invested on a personal and professional level in making sure he has a healthy future. I want treatment for him as he grows older to look vastly different and less invasive than what I have had to go through or what my patients are having to go through.

The advice I would give to a newly diagnosed NET patient is, first of all, take heart, you're not alone. The psychological burden of being diagnosed with a rare illness, and I can speak to this personally, is that you feel unique in a bad way. You feel like you're the only person to go through this. That's obviously a bit histrionic, but that is how it feels at first.

Then what you discover, especially online, and again, there's good and bad things about social media and search engines, that is there are other people like you, perhaps much more like you than you may have realized. So I would encourage them to carefully seek out online community and support.

Then finally, I would ask them to vet information. We are pretty good these days at rating things, meaning that I can go on my phone and decide where I want to eat tonight based on a restaurant review. People should be as discerning when it comes to medicine and research. Again, the first thing that pops up in your Google Search may not be reliable, and it does take some time and experience to separate the wheat from the chaff. Dr. Google is a dangerous, dangerous thing because it's a free search engine, but what's not free are the way the results are privatized. People can pay money to have their results rise to the top, often for profits. So they're not necessarily serving you the best

treatment. They might be serving you the treatment that's in their best interest.

As a patient, and as a parent affected by NETs personally and in my family, I am very grateful and hopeful. That's one of the best things you can say I think in oncology. We're sometimes viewed as very pessimistic. I would argue the opposite. I think we can see how far we've come. We still have a long way to go, but there's real progress occurring here and hereafter, and that should spark hope."

Something to keep close to your heart in all of this is don't panic. Take your time and get informed. Don't rush to treatment before you've really learned about what's going on and why.

Here's **Dr. Blase Polite**, a clinical oncologist at the University of Chicago:

Polite: *"Any cancer diagnosis, certainly neuroendocrine is one of those, is almost never a medical emergency, right? There are exceptions, but a cancer diagnosis is almost never an emergency. It's an URGENCY, but it's not an EMERGENCY, and you have time to get to the right place, to the right center, to the right group of people looking at things. And as you see all this information, all the things that we have to think about, how important it is that we can talk to each other, do tumor boards, if we have to call to our colleagues across the country, do those type of things, to make sure that we put a plan in place for you that makes the most sense."*

You're going to be presented with many opinions and many options. And in the end, the course of treatment you want to pursue is going to be your decision. It's important that you feel good about the doctors you end up choosing, that you like them, and trust them, and feel that you can ask them questions and get meaningful answers.

Creamer: *"You want to be able to have a comfortable relationship with them, make sure that they're kind of hearing you, and to make sure that*

everything is being laid out for you so you have a good understanding of things."

Nakakura: *"Getting as many opinions as possible is critical, to be fully informed of what your options are, realizing that there is no one right answer. For example, you may go to one institution, they may say, "surgery!" You may go to another institution, they may say, "never surgery!" And you have to listen to the pros and cons, or the arguments made in favor or not in favor of an intervention (or treatment), and decide for yourself what do you feel is right for your body and yourself, based on the information you've been provided."*

We are going to spend the next several episodes talking about all of the major treatment options currently offered for NET patients in the United States. It is our hope that by listening to this series and reviewing our additional online resources, you'll continue to learn about NETs and better understand the disease that you're living with and dealing with, emerging as a listener who is NET wise.

Thank you, listener, for tuning into NET Wise. My name is Laran Hyder. I'm the Director of Education and Outreach for the Neuroendocrine Tumor Research Foundation. I executive produced and co-wrote this series. It was produced and co-written by David Hoffman of CitizenRacecar. This episode was made possible by the generous support of Advanced Accelerator Applications, a Novartis Company, Lexicon Pharmaceuticals, and the Vincent E. Taylor Patient Education Fund. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. This is a production of the NET Research Foundation. We're committed to improving the lives of patients, families, and caregivers affected by neuroendocrine cancer. We fund research to discover cures and more effective treatments, and we provide information and educational resources. Please visit us at NETRF.org

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