Episode 28
Nuclear Medicine for NETs:
Transcript

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

In this episode, we're going to talk in depth about one of the most exciting and widely discussed treatments for NETs: PRRT.

This is a revised version of an episode that originally came out in 2020. A lot has happened since then in the development of nuclear medicine treatments like PRRT, and we're excited to be able to bring you information that is updated and current.

But let's start with the basics: what exactly *is* PRRT?

PRRT stands for Peptide Receptor Radionuclide Therapy. In simple terms, this is a nuclear medicine treatment that uses targeted radiation to kill NET cancer cells from within.

Here's how it works:

Some NETs have proteins on their cell surface called receptors. These receptors can attach to hormones, like somatostatin. You might remember that in episode two of this series, we talked about somatostatin and its tendency to seek out and bind to these receptors.

This biochemical pathway is an important part of DOTATATE PET-CT scanning. And PRRT makes use of this exact same biochemical pathway.

But instead of binding to a cancerous cell so it can be seen on a scan, PRRT uses this pathway to deliver radioactive compounds called radiopeptides that *destroy* cancer cells.

Here's Dr. George Fisher, an Oncologist at Stanford University:

> ***Fisher:*** *"By the same- completely the same- concept where you're delivering a radioactive dose that can be imaged by a PET scanner. You can now deliver a radioactive dose that can kill any cell that's adjacent to where it lands. So instead of using a radioactive isotope that's just hot enough to see with a scanner, you can use a radioactive isotope that's hot enough to kill adjacent cells. It's giving off radiation that is intense enough to destroy cells within a millimeter or two of wherever that lands. And if enough of those cells have this Somatostatin receptor that can bind to the drug, and if you give enough of the drug, with radiation linked to it, then you can kill a fair proportion of tumor cells. Now, unfortunately that's not a cure, but it can halt the growth or even shrink the tumor and sometimes keep it shrunk for years."*

Dr. Xavier Keutgen is a surgeon at the University of Chicago:

> ***Keutgen:*** *"My opinion about PRRT is that it's very helpful, especially in stabilizing the disease burden in patients that cannot have surgery or are not good candidates for other therapies. And, I would even argue that PRRT is the next best therapy if surgery is not an option."*

Here's Dr. Courtney Lawhn Heath, a nuclear radiologist at the University of California, San Francisco.

> ***Lawhn Heath:*** *"When I was a radiology resident, I, and I learned about PRRT, I just thought, I couldn't imagine anything more elegant in terms of the concept behind this therapy, right? The idea that something could go in the body like a heat seeking missile, and just seek out tumors and ignore everything else, right? And just treat the tumors, but not just, not just treat one or two tumors, but every tumor that a person might have, as long as it's expressing the right receptor, as long as it's lighting up on PET, it could be treated by this treatment."*

When PRRT first came on the scene, it was viewed as an exciting treatment option for NET patients. But it wasn't always available to patients in the U.S.

The treatment was developed in Europe, and its use there increased throughout the early 2000s. Soon, clinicians in The Netherlands, Germany, Switzerland and Italy were treating patients from all over the world.

Here's Josh Mailman, a NET patient and advocate who's a world authority on PRRT for NETs:

> ***Mailman:*** *"In Europe, these things are done center by center, with different protocols and no standard protocols. The early 2000's the first Phase II trial is done, which really tries to have some standard protocol and that turns out to be an international trial that includes the U.S. and*

it was successful, but the company that did the trial decided not to go forward. And so we have a patchwork of places around the world, whether it's in Europe or Australia or India and even a little in the U.S., using their own protocols, their own methods, reporting their own stuff retrospectively and really with not the type of evidence that oncologists use to prescribe a treatment.

So while it's commonly thought that it was approved in Europe much earlier, it really was only by about six months."

During that time, some American patients sought out treatment in other countries. Through persistence and personal resources, they were able to find a place where PRRT was offered, be accepted there for treatment, and travel there at their own expense.

One popular destination was a nuclear medicine clinic in the town of Bad Berka [bahd burk-uh], a spa resort in central Germany.

Murfin: *"My name is Gary Murfin. I live outside of Seattle, Washington. I was diagnosed in 2008. My diagnosis was a primary of the ileum with NETs to my liver and to my sacral bone and to some adjacent lymph nodes. And within a month, I had a resection of the primary and a right hemicolectomy and they took care of some of the NETs that were in my lymph nodes.*

And I didn't have to do anything about the liver. And, of course, there wasn't - at that point in time - wasn't anything to do about the sacral lesion I had as well. In the course of all this, I ran across some patients who had been treated with PRRT and they had been treated in Bad Berka by Dr. Baum, by Richard Baum.

And that fascinated me because I had an extra hepatic disease with the sacral lesion. And so I started researching PRRT.

We're talking about now May, June of 2009. I learned more about PRRT and felt that that was possibly applicable, you know, in my case. In late June of 2009, I actually initiated a phone call with Dr. Baum in Germany, and he said, well, send me your records.

It just became, that I could go to Germany and get this, and that was confirmed by Dr Baum. The downside was insurance was not going to cover it. I mean, I knew that going in, so the onus was on me to get there and to pay for it, but I thought it was an option that I needed to consider.

My first one was in 2009. In 2011, I went back for, uh, a gallium scan and they found some progression. So in 2011, I had my second. And it was not until September of 2017, a six-year hiatus, that more progression was found. And at that point in time they said the progression was such that we really need to treat you twice. So two months later, in November, I had my fourth treatment. And that really constituted the full repertoire, so to speak, of my treatments until the fall of 2018 when I actually for the first time started on Lanreotide as a somatostatin receptor, uh, medication.

I'm doing pretty well. Actually, my cancer has never really affected me as much as it has a lot of other patients. I was diagnosed when I was 66, and now - now I'm 77 going on 78. I go and do things. I don't have any… the cancer's not holding me back."

While Gary Murfin was undergoing his PRRT treatments, a multinational Phase 3 clinical trial was underway.

The trial, called NETTER-1, launched in 2010. It compared PRRT with the current standard of care.

Close to 80 percent of patients in the study who received PRRT went longer periods of time without tumor growth. And thirteen percent of *those* patients experienced complete or partial tumor shrinkage.

Those results were published in 2017, and in 2018, the U.S. Food and Drug Administration approved the use of PRRT for midgut NETs.

Here's Dr. Ed Wolin, an Oncologist at Mt. Sinai in New York who was involved in the study:

> ***Wolin:*** *"Survival looks like it's better with PRRT. Not only does it control cancer and keep it from growing, but it makes people feel better. The majority of patients had control of diarrhea, control of flushing, control of tumor related pain, like liver pain and bone pain, increase in energy level, increase in general level of performance and activity and improvement in health score by standardized tests of quality of life that patients would fill out in questionnaires."*
>
> ***Lawhn Heath:*** *"it's been sort of surprising to see what a game changer PRRT has really ended up being. Um, at least, you know, I'm speaking from my perspective as a, as a practitioner in the United States. It went from, You know, we went from sort of a side thing that you were lucky if you could be able to access to PRRT now being one of the absolute standard pillars of treatment of well-differentiated neuroendocrine tumors."*

And if you're a NET patient curious about how PRRT might fit into your treatment, here's what you should know.

First: you have to be a good candidate for PRRT.

That means other treatment options have been ruled out. It also means that there are enough tumors throughout the body to justify the treatment – PRRT is safe and effective, but it's not something that can be repeated over and over.

And most importantly, you can only be a candidate for PRRT if your NETs have active somatostatin receptors.

Here's Dr. Aman Chauhan. He leads the Neuroendocrine Tumor Program at the University of Miami:

> ***Chauhan:*** *"It only works if you have somatostatin receptors in your body. It works better if the receptor density is higher in the tumors."*

Around 80 percent of all NET patients have tumors with these receptors. If you're in the other 20 percent, this treatment will have no impact at all.

An effective way to determine how many receptors your particular tumors have – and how active they are – is by using a DOTATATE PET-CT scan.

> ***Chauhan:*** *"So somatostatin receptor imaging is a very critical aspect of us evaluating the patient. And if we see a lot of hotspots in the scan, then we feel comfortable that PRRT might work in that particular patient for that particular scenario."*

Here's Dr. Richard Baum, a nuclear medicine specialist in Germany. He's the doctor who treated Gary Murfin, whose story we heard earlier:

> ***Baum:*** *"And we can not only look at images and say the receptors are there, but we can also quantify the number of receptors by a number, which is called standardized uptake value. So it's not only a subjective impression you have, but it's an objective measurement you can do with PET/CT and say the SUV, the number of receptors on the tumor cells is high enough or which qualifies a patient for a PRRT, or it's not high enough."*

Because this treatment uses radioactive compounds, doctors work to ensure your body can tolerate it without too many side effects.

> ***Chauhan:*** *"So I like to have a sit-down with the patient and discuss their history and physical examination. What all treatments has this patient experienced and been treated with in the past? PRRT as of now is not the front-line treatment, so it is important to know what all treatments have patients progressed on. It is also important to know what's the baseline bone marrow functions. Patients should have good blood counts and renal functions because PRRT can affect renal issues."*

Here's Dr. Rathan Subramaniam. He's the Executive Dean of the medical school at the University of Notre Dame in Australia:

> ***Subramaniam:*** *"And then the liver functions - because a liver functions can get affected during the treatment because many patients would have liver metastases. So we're establishing baseline metrics of these three organs, the kidneys, the bone marrow and the liver, before we go ahead and treat these patients."*

If you and your care team decide to go ahead with a course of PRRT, here's what that might look like.

> ***Lawhn Heath:*** *"PRRT is done typically in four cycles, each spaced out by eight weeks. So the whole process, all four cycles, takes a minimum of six months. So you have cycle one, and then eight weeks later, cycle two, etc, etc. And so what one cycle looks like at most centers, it is just one day."*

Here's Karen Ohara, Research Coordinator at Rush University in Chicago:

> ***Ohara:*** *"The average time from arrival to a facility to discharge is about seven-to-eight hours. So you arrive around 7:00, 7:30 in the morning. We go ahead and take your vitals. Um, one of the things we do during the course of the treatment is monitor your vitals - blood pressure, heart rate and so forth. The nursing staff will put in an I.V. catheter, it's done peripherally in a vein in your arm and all of the medications will be coming through this one area."*

Each of these infusions comes in two parts: first are amino acids to counteract any negative effects of the radiation. Then there's a medication called Lutathera, which contains the radioactive particles.

> ***Subramaniam:*** *"we give an amino acid solution to protect the kidneys so that when these radiotracer is excreted through the kidneys it'll cause minimum damage. That amino acid solutions, um, go through about anybody in four-to-six hours. And about a half an hour into the amino acid solution, we start the Lutathera. Most of the time, patients are lying in a bed or sitting in a chair - however they feel comfortable, and they probably won't feel anything as these infusions going through. And then early afternoon - midafternoon, we would finish the amino acid infusion, and then they usually go home."*

> ***Lawhn Heath:*** *"Generally, people feel pretty well during the infusion. In the old days, the amino acids that were used were actually, it was a different formulation that actually caused horrible nausea.*
>
> *So it wasn't the PRRT that was causing it, but the amino acids that are trying to protect the kidneys caused horrible nausea and vomiting. And so everybody got anti-nausea medicine.*
>
> *In this day and age, we have a much more concentrated form of amino acids. In other words, it's only the ones, it's only the little amino acids that are helpful for protecting the kidneys. And it doesn't include any of the extra randos in there. And, uh, since using those more, that more sort of specific, specifically formulated version. We've had almost no cases of nausea related to the amino acids."*

At many centers, a PRRT treatment just consists of that one-day infusion. But at some, there's also an imaging component.

> ***Lawhn Heath:*** *At our center, we have patients come back the next morning. So about 24 hours after they get their PRRT for an imaging study. And that imaging study is called a SPECT CT.*

This is similar to a PET scan, but it doesn't require putting anything else in your body – radiologists can take an image of the PRRT itself.

This allows doctors to measure how much radiation went to each tumor, as well as where else in the body radiation may have ended up.

This works because PRRT is radioactive – and by the way, because PRRT is radioactive, you also become radioactive. This lasts for several days after each treatment. And there are some protocols

that you have to follow to prevent exposing other people to unhealthy doses of radiation.

Marilyn Kline from San Francisco was kind enough to speak to us while she was in the middle of receiving PRRT:

> ***Kline:*** *"It's a big production. You have your own bathroom and it's covered - the walls are covered with paper and, you know, the toilet seats covered with paper, and there's a big tape that says 'do not cross', and I'm the only one allowed in there for the duration of it. And then to flush the toilet twice and clean it with a Clorox bleach wipe every after every time I use it. And there are protocols they tell you when you go home, you know. I'll be wearing the same clothes for the next couple of days, and then I will wash all of that separately after three days. The protocols in my healthcare system are three days that I stay three feet away from everybody, and then seven days to stay three-feet away from pregnant women and children under 10."*

While you're between PRRT sessions, you're also given a document that explains the treatment.

> ***Ohara:*** *"If you're in a public area, I guess law enforcement these days also have some, you know, some of them actually do monitor, um, for things like this. So it's good to carry this letter around."*

Because of that radiation concern, many patients elect to stay out of their houses for three-to-five days after each treatment. Especially if they have children or a partner who is pregnant, or who live with elderly people.

For new mothers, it's recommended that they hold off on breastfeeding for an additional two-to-three months after the

final infusion. And women are encouraged to not get pregnant for at least six months afterwards.

Despite those complications, many patients report that these treatments are relatively easy to tolerate – much less uncomfortable than surgery or some other medical treatments.

> ***Kline:*** *"It's remarkably easy, actually… Compared to chemo, it's remarkably easy."*

And despite the short-term drama of those radiation protocols, the risk of negative long-term effects of the treatment seem to be small.

> ***Fisher:*** *"The damage to any particular tissue is a function of how potent that radiation is – the strength of the radiation, and how long it's next to that tissue. So as long as it's cruising through the blood and going by tissues rapidly, it's not doing a whole lot of damage. But if it sticks to something and stays there, that's where it does the damage. And because this is sort of special Velcro in the tumor that attaches to the Velcro on the radioisotope, it just sticks there and then it delivers that radiation set. Radiation sits there, right on the tumor. It's a tumor that gets most of the damage.*
>
> *You just pee it out so you have radioactive urine when you're making this and you have to dispose of it in a certain way. But that's perfectly fine."*
>
> ***Baum:*** *"And there are actually only two areas where PRRT might cause damage. The one is the bone marrow, okay – especially in patients with a heavy involvement of bones with metastatic disease, with bone metastasis. And, um, we have seen in our long-term follow-up only one really serious adverse effect, which is called MDS, myelodysplastic syndrome, which might be caused by the*

radiation itself. But this happens in less than 3% of the patients according to our analysis. And also according to other European data, for example, from Italy, with the long-term follow up.

And the second is actually the kidney. And we recently have reported our data in more than 4,400 treatment cycles with a follow-up of up to 18 years, and we have not found any – not found any – serious renal damage using lutetium.

Other adverse effects are very mild or, you know, just for a few days a patient might feel some more fatigue from the treatment, or there might be increasing symptoms like flushing after treatment. Okay, and very rare there are carcinoid crisis under treatment and other things which can happen. But compared, for example, to chemotherapy, the overall adverse effects are very rare and the treatment is very well tolerated."

Here's Dr. Blase Polite from the University of Chicago:

Polite: *"If we've talked about sequencing of therapies, we have to be careful. Some of our drugs like temozolomide also have bone marrow toxicity. We don't know ultimately how drugs like temozolomide and things like lutetium are going to play out together, so these are things again we have to be aware of, we have to watch out for, and you know, you all should know about."*

Because PRRT can be well-tolerated and can have such positive effects in some patients, there has been an increasing demand to use it for other NET cancers. Right now, it's only approved in the U.S. for gastrointestinal and pancreatic NETs.

But clinicians have seen encouraging results with some other NETs – lung NETs for example. That's shown in data captured from off-label use and use in other countries.

> ***Wolin:*** *"There's a challenge right now in the United States because the FDA approved neuroendocrine tumor treatment with PRRT for people that have gastro-entero-pancreatic neuroendocrine tumors, that's the word they used. So neuroendocrine tumors that start in the gastrointestinal tract or pancreas, they didn't use the word "lung". So what do you do when somebody has a strong somatostatin receptor-positive tumor that starts in the lung? We beg and plead with insurance companies. We try to get approval. We try to see if there's clinical trial they would qualify for. Some way or other, we try to get treatment, because as far as I'm concerned it's a potentially very effective treatment and is something that we should be able to have available, but it's more challenging."*

There's also discussion among surgeons about whether PRRT's ability to shrink some tumors might make it a useful precursor to surgery on liver metastases. But this is still being studied.

> ***Keutgen:*** *"And we're trying to figure this out, so there are reports where PRRT has shrunk the primary tumor and sometimes it had also shrank the liver metastases. So patients that were unresectable could become resectable with PRRT, and we need to look in to this a little further."*

But in most patients, PRRT only *pauses* tumor growth – it rarely shrinks them. And it never causes them to disappear completely.

> ***Keutgen:*** *"The real fantastic and strong role for PRRT is at stopping tumor growth when Octreotide cannot do it anymore, and occasionally PRRT can do this for many, many years.*
>
> *So you're not going to get PRRT because we think the entire tumor is going to disappear and we're going to cure you with it, but you're going to get PRRT when Octreotide*

cannot control the tumor growth and when surgery is not an option, uh, because it will stabilize the disease, probably for many years. And as I said, occasionally it may even shrink the tumor."

PRRT is far better tested and understood than it was when we originally published this episode. But it remains relatively new, and there's still a lot of research being done to try to make it better.

Lawhn Heath: *"I think the way that is probably the most on the, on the tip of our tongues right now in the neuroendocrine space, that people are the most excited about, is to change the type of radiation that is used.*

So the isotope, the radioactive isotope that we use in our standard current PRRT in the U. S. is lutetium 177. And the way that that Lutetium 177 isotope has its therapeutic effect is that when it has its radioactive decay, it emits what are called beta particles. What we're looking at now in the field is using different isotopes, ones that, instead of emitting beta particles, emit alpha particles."

Alpha particles are substantially larger than beta particles, and when they hit their target – like a tumor cell – they have a much bigger impact. Not only that: the nature of alpha particles may also make it so they have fewer effects on the bone marrow and kidneys.

Lawhn Heath: *"So the idea here is that at least in theory, these alpha therapies may do more harm to the tumors. And potentially less harm to the sort of innocent bystander tissues like the bone marrow. That is the hope. That is how it's looking right now in some of the clinical studies that we've seen come in from outside the U.S. And now what we're very excited about is that, uh, now one of the big trials has finally come to the U. S. where, you know, that will*

hopefully lead to the FDA approval of this new agent. Again, assuming that it proves to be as as effective as advertised."

The alpha-emitting agent in this new PRRT treatment is called Actinium-225 DOTATATE.

> ***Lawhn Heath:*** *"Actinium 225 is not the only alpha emitting isotope. It's one of several actually that are being looked at. But the big trial, the one I think is going to be more likely to be accessible to people from all over, is of this actinium PRRT agent. The name of the trial is the ACTION-1 trial, and it's actually an international multi center trial."*

Researchers are also working on new ways to use a kind of medication called P-A-R-P or "Parp" Inhibitors to increase the amount of somatostatin receptors a tumor expresses, to make treatments like PRRT more effective in more patients.

> ***Lawhn Heath:*** *"The enzyme PARP is involved in DNA repair and the way PRRT works is that the radioactive particles Damage the cells DNA and if enough of that damage happens eventually it will overcome the cells ability To repair itself and the cell will die.*
>
> *So you you have PRRT that damages DNA And then you have a PARP inhibitor. So you're inhibiting an important enzyme that, that allows tumor cells to repair their DNA. So you're essentially damaging the DNA and then stopping the tumor cells from being able to repair the damage. That's a pretty elegant combination. And there are some prospective trials of that going on right now."*

Here's Dr. Rodney Hicks from the University of Melbourne in Australia:

> ***Hicks:*** *"Opening the therapy up to patients who have much lower levels of somatostatin receptor expression, if we can further sensitize the cells by using a PARP inhibitor, we expect that this will make it a more effective therapy, particularly in those patients. The benefit I think will be two-fold, uh, of this approach. One is opening it up to patients who would otherwise be unlikely to respond - those with lower expression of somatostatin receptors, which is around 15-to-20% of patients. Also, I think it's going to increase the effectiveness in a group of patients in whom despite appearing to be suitable for the therapy, and we give multiple cycles of treatment, and their tumors don't seem to respond."*

These developments are just the beginning of years of research that will go into improving PRRT.

> ***Lawhn Heath:*** *"Many of the new types of therapies that we're looking at are ones that are designed not to just to sort of be also-rans, or to, I don't know, make pharmaceutical company X, you know, more money, but be similar to this other drug that's patented in this other way. But rather, we're really looking at compounds that either help people overcome resistance to the therapies that we're using already.*
>
> *And so potentially expanding the population of patients who could benefit from these therapies. That's what's the most exciting thing to me. And we've, we talked about alphas as well as combination therapies, but there are some other changes and modifications coming down the pipeline that again, I'm hoping will really expand the population of patients who can benefit from PRRT."*

This episode is dedicated to the memory of Marilyn Kline, who passed away during the production of the original episode.

Thank you for listening to NET Wise. I'm Jessica Thomas, Director of Patient Education for the NET Research Foundation.

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