NETWise
A Podcast About Neuroendocrine Cancer

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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.

In this episode, we're going to talk about one of the most promising treatments currently available for NET cancers – one that just became approved for use in the United States about two years ago, and is the subject of much hope, discussion, and debate in the NET community - Peptide Receptor Radionuclide Therapy, or PRRT. In simple terms, PRRT is a nuclear medicine treatment that uses targeted radiation to kill NET cancer cells from within.

Some NETs have proteins on their cell surface called receptors, they can attach to hormones, like somatostatin. PRRT targets these somatostatin receptors using radioactive compounds called radiopeptides. In episode two of this series we talked about somatostatin and its tendency to naturally seek out and bind to somatostatin receptors. This biochemical pathway is an important part of Gallium-68 Dotatate PET-CT scanning. PRRT uses this exact same biochemical pathway, but instead of only binding to a cancerous cell and lighting it up so we can see it better on a scan, PRRT uses that mechanism to deliver certain radiopeptides to actually destroy cancer cells. In the U.S., Luticium 177 is often used.

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 a way of delivering radioactivity, a nuclear bomb right to*

the tumor cell. Literally a nuclear bomb – 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 links 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."

And here's Dr. Xavier Keutgen, a Surgeon from the University of Chicago:

Keutgen: *"My opinion about PRT 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 PRT is the next best therapy if surgery is not an option."*

When PRRT was first tested in Europe in the early 2000s, it achieved an almost mythical status as a potential cure that was widely available to patients elsewhere but being denied to people in the US. This was not the case – it wasn't widely licensed anywhere at the time, but it was more available in Europe because of different policies there regarding what's called "compassionate use"

Here's Josh Mailman, a NET patient and also an advocate who is 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. What was going on in Europe prior to that and the rest of the world was really compassionate use of the product in different countries

have different rules for compassionate use of drugs that aren't approved."

Some American patients, through persistence and personal resources, were able to find a place where this treatment was offered, be accepted there for treatment, and travel there at their own expense.

Murfin: *"My name is Gary Murfin. I live outside of Seattle, Washington. I was diagnosed in 2008. My diagnosis was a primary of the ilium 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 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 Lanriotide as a somatostatin receptor, uh, medication.

I'm doing pretty well. Actually, my cancer is 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."

PRRT was finally officially approved for treatment of gastrointestinal and pancreatic NETs in adults after the completion of a landmark study called NETTER-1. NETTER-1 was a large Phase 3 clinical trial comparing PRRT with the standard of care. Close to 80 percent of patients receiving PRRT in the study went longer periods of time without tumor growth. Thirteen percent of those patients experienced complete or partial tumor shrinkage.

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

Wolin: *"Survival looks like it's better with PRRT. The other thing that was just reported this past year was a study that we did on quality of life in a patient with NETTER-1 - that 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."*

And since this treatment was approved for more widespread clinical use, doctors around the world are seeing promising results with NET patients. It's also showed encouraging results for patients with hormonal disorders caused by NETs, like Carcinoid Syndrome:

Fisher: *"Because if the carcinoid syndrome is due to hormonal syndrome, if that's due to the release of hormones from numerous cells and you, you just cut down the cell number by 50%, then you're going to make less of the hormone and that person might not have the syndrome anymore."*

> ***Mailman:*** *"Currently in the United States we're seeing over 150 centers that probably are doing a thousand-ish treatments a year using this new drug. And this is now spurring other studies in neuroendocrine tumor cancer patients for using these types of radio label drugs. And also other disease using other types of peptides like prostate cancer, and they'll use what we learned in NET patients to really benefit other cancer patients using targeted agents as well, but it was all led by neuroendocrine tumor patients."*

It's very important to remember, though, that this treatment only works on NETs that have active somatostatin receptors, which is somewhere around 80 percent of all NET patients. If you're in the other 20 percent, this treatment will have no effect at all.

Here's Dr. Aman Chauhan, head of the PRRT program at the Markey Cancer Center at the University of Kentucky:

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

An effective way to determine how many receptors your particular tumors have and how active they are, is by using a Gallium-68 Dotatate PET-CT.

> ***Chauhan:*** *"So somatostatin receptor imaging is a very critical aspect of us evaluating the patient. So, we routinely do gallium Dotatate scan and in common terminology, we call it NETspot. And if gallium scan is positive, 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:

> **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 PRT, or it's not high enough."

Because this is a nuclear medicine treatment, using radioactive compounds, doctors work to ensure your body can tolerate the treatment with few 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 a 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, Dean of the Otago Medical School in New Zealand:

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

Once it's decided that PRRT is the right course of action, the treatment currently being practiced in the U.S. consists of four infusions, each one taking almost a full day to compete. 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 on your arm and all of the medications will be coming through this one area."*

Each of these infusions comes in three parts – a medication to control nausea, amino acids to counteract any bad effects of the radiation, and then a medication called Lutathera, which contains the radioactive particles.

> ***Subramaniam:*** *"We give an antiemetic so that we decrease the chance of nausea and vomiting. So it'd be infused that first – it probably takes about couple of minutes. And then, 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 in about anybody in four-to-six hours. And about a half an hour into the amino acid solution, we start the Lutathera, which probably takes about 35- to-40 minutes all in all. So 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."*

This process is then typically repeated three more times, eight weeks apart.

An interesting aspect of PRRT is that because this treatment is radioactive, while you're receiving it, you also become radioactive for several days after each of those treatments. There are some pretty intense protocols that have to be followed to prevent exposing other people to unhealthy doses of radiation.

Marilyn Klein 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. For instance, what I told you as we were planning this session, we've got to stay three feet away, right? So that's one of the protocols. The other is all the clothes that 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 who have children or a partner who is pregnant, or who live with elderly people, elect to stay out of their houses for three-to-five days after each treatment. 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 actually relatively easy to tolerate – much less uncomfortable than surgery or even some 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 while you're undergoing these infusions, the risk of negative long-term effects of the treatment seem to be extremely small.

> ***Fisher:*** *"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 the 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 a large and increasing demand to use it for NET cancers other than the gastrointestinal and pancreatic NETs for which it's been approved for use in the United States. Clinicians have seen encouraging results with lung NETs, for instance, in data captured from off-label use and use in other countries.

Here's Dr. Thor Halfdanarson from the Mayo Clinic in Minnesota:

Halfdanarson: *"PRRT Lutathera does NOT have an FDA approval for pulmonary or lung neuroendocrine tumors It wasn't really studied that way, but there is definitely a lot of*

data out there. We have a review article in the making with looking at PRRT and lung tumors. There is no question it works."

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-enteral- 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 sometimes."*

There's also much discussion among surgeons about whether PRRT's ability to shrink some tumors might make it a useful precursor to surgery on liver metastases. This is still being studied, though, and still speculative.

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."*

For all the positive effects PRRT may have for some patients, it's really important to remember that it's not a magic bullet. It only works in patients that have strong somatostatin receptors on their tumors. And even then, in most patients it only pauses tumor growth – it rarely shrinks tumors, and never causes them to disappear completely.

Keutgen: *"PRRT is a very hot new treatment tool, but it is a tool that we need to use when you need it most. 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 - in one-out-of-four or one-out-of-three patients, it may even shrink the tumor."

And as research continues, PRRT is evolving to find new ways use the same basic biochemical pathway

> ***Mailman:*** *"Having a crystal ball is especially hard, especially about things in the future, and that's where we are with what's next in PRRT. There's several directions that this can take."*

Some of these new directions involve different radioisotopes. One of these is an isotope of the element Yttrium, called Y-90, which is stronger- more radioactive – than lutetium 177. This, of course, makes it more challenging to work with.

Here's Dr. Tom Hope from the University of California, San Francisco:

> ***Hope:*** *"We're using Yttrium 90, or Y 90 instead of lutetium 177. So we're using Y90 Dotatoc. And Y90 has a couple of characteristics which are different than lutetium that will make it more effective in treating tumor but also carry more toxicity risks associated with it."*

> ***Mailman:*** *"Lu177 is great, has a very small pathway, can harm less cells, less healthy cells nearby it, but doesn't necessarily have a really great kill pattern of killing the cells because of a lower energy. Y-90 has a much higher kill zone, but it's actually also has a much wider path and can get some cells that we probably don't want to include."*

One of the ways researchers are trying to mitigate this additional potential for harm to healthy tissues is by injecting it directly into the area of the body that contains the majority of the tumors, rather than letting it travel through the whole bloodstream.

> ***Hope:*** *"With the technique that we're using, we actually put a catheter into the artery that feeds the liver and administer the Y90 Dotatoc directly into the liver. And the rationale for that is that when you put it directly into the liver, and you have a bunch of metastasis in your liver, those metastases will absorb the dose on the first pass, the first time the dose goes through your liver, at a*

higher fraction or higher concentration than if it were given through the vein in the arm."

Other new isotopes being explored are in a class called "Alpha Emitters", which we'll talk about in a future episode.

Also, researchers are working on developing 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.

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."*

Some of these new directions are still experimental, though, and will continue to be tested before becoming widely available.

Mailman: *"So we really mean to understand this using clinical trials where we can understand what the outcomes really are and how this really will impact patients. Because really we're always balancing the risk and reward. While it may be really great at killing tumor cells, we have to make sure that we're not getting anything else as a byproduct. So work is underway and it will take several years to get this done."*

But because the currently available version of PRRT has been shown to work so well in so many NET patients, with so few side effects, it's extremely likely that it will be used more and more often, and earlier in the course of treatment.

Mailman: *"I think now that we have the data from NETTER-1, we have this wealth of patient reported outcomes, or PROs,*

that we will see this earlier in the treatment paradigm rather than later, because it is a fairly easy treatment to take, and it has really shown to give a good quality of life for a long period of time. So I think it will move up earlier in the treatment paradigm. But I never…I don't imagine going to overtake using somatostatin analog first to see if you can control the disease."

So far in this series, we've looked at many of the most important treatments for NETs – but we haven't yet discussed medical treatments like somatostatin analogs and mTOR inhibitors, and traditional chemotherapies. And how do all these different kinds of treatments fit together into a course of treatment – a plan for managing your particular NET for as long as possible?

All of that and more, next time on NETWise.

This episode is dedicated to the memory of Marilyn Klein.

Thank you for tuning into NET Wise. My name is Laran Hyder. I'm the Director of Education and Outreach for the Neuroendocrine Tumor Research Foundation and serve as executive producer and co-writer of this series. It was produced and co-written by David Hoffman of CitizenRacecar.

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