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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.

One of the things that sets neuroendocrine tumors apart from other kinds of cancer is that they can occur almost anywhere in the body. Those different locations -- or primary sites -- can mean the NET takes on different characteristics, and requires different kinds of treatment.

In previous episodes of this show, we've talked about lung NETs, pancreatic NETs, small bowel NETs, and gynecological NETs.

Today, we're going to be talking about skin NETs. These are known as Merkel cell carcinomas.

Silk: *Merkel cell carcinoma is an extremely aggressive cancer of the skin. It can double in size in just a few weeks.*

Dr. Ann Silk is a medical oncologist at Dana-Farber Cancer Institute, where she co-directs the Merkel Cell Carcinoma Center for Excellence.

Silk: *It's also so rare that many doctors and patients are caught off guard when they're diagnosed.*

If this is you, we hope listening to this podcast will help. We'll talk through diagnosis, treatment options, and some current areas of research.

Because of how rare and aggressive it is, Merkel cell carcinoma is very different from other forms of skin cancer, like basal cell carcinoma and squamous cell carcinoma.

Dr. Manisha Thakuria is a dermatologist who works at Brigham and Women's hospital and Dana-Farber Cancer Institute. She co-directs their Merkel Cell Carcinoma Center, along with Dr. Ann Silk.

Thakuria: *Merkel cell carcinoma is an extremely rare form of cancer. It affects about 2,400 patients in the U. S. per year. If you compare that to other cancers, you know, basal cell carcinoma, squamous cell carcinomas, those affect hundreds of thousands or probably millions of patients a year. In fact, it's not countable. Those are actually the two cancers that are not even counted in national cancer registries because they are so common. So that's one way that it's different.*

Another way that it's different is that Merkel cell carcinoma really has this propensity to rapidly spread, through lymphatic vessels and go to lymph nodes, or it can spread through blood vessels and go to, you know, really

any organ. And most skin cancers don't like to do that. So basal cells, squamous cell carcinoma— the vast majority, you know, way more than 99 percent of basal cell carcinomas, probably about 95 to 96 percent of squamous cell carcinomas, those are going to be cured with surgery or even sometimes certain procedures that are less invasive than surgery. Whereas Merkel cell is very much a more dangerous cancer, pound for pound.

And Merkel cell carcinoma isn't just different from other skin cancers – it's also different from other NETs.

Thakuria: *Most neuroendocrine cancers are slow-growing. And most neuroendocrine carcinomas, their mortality rates are just not as high, unfortunately, as Merkel cell carcinoma. So that's like a key difference actually, is that this is a neuroendocrine carcinoma that actually has fairly rapid behavior, in terms of its ability to spread.*

Another big difference is in the name. Most other NETs are named for the organ where the primary tumor is located. But skin NETs are named after Merkel cells – which is a bit complicated.

Dr. Paul Nghiem is on the faculty at the University of Washington in the dermatology department. He runs a research lab there, and takes care of patients with Merkel cell carcinoma.

Nghiem: *So Merkel [has] historically been called neuroendocrine carcinoma of the skin. And it just so happens that the normal skin cell that is neuroendocrine is a Merkel cell. And a Merkel cell is named after a German anatomist who identified them a long time ago. And they are touch cells. So when you stick your finger in your pocket and you feel sandpaper or you feel silk, it's your Merkel cells, which are at very high density on your lips and on your fingertips, that are telling you this sense of fine touch. And the cancer looks like the Merkel cell in the skin. It's not at all clear— in fact, we don't really*

believe that the normal Merkel cell is turning into the cancer.

Thakuria: *I don't know that we really know what the cell of origin is for Merkel cell carcinoma, but most people in the community believe that it comes from an epidermal stem cell. It doesn't matter clinically, really, where it came from. And so, although there's a lot of debate, it's sort of like, it's debate for scientists, but it doesn't affect our clinical care of patients.*

Nghiem: *Basically Merkel cell carcinoma is a neuroendocrine carcinoma that just arises in the skin.*

We do know something about what causes Merkel cell carcinoma. Like all cancers, it starts with a glitch in the DNA of a cell, causing uncontrolled growth. There are two known causes for this kind of cancer:

Silk: *One of them is an accumulation of UV damage, which leads to cancer through an accumulation of mutations from the sun. The other way that Merkel cell carcinoma can be caused is through a virus called the Merkel cell polyomavirus. That virus can get into a cell and turn it into a cancer cell.*

The biology of these two types of Merkel cell carcinoma are different, but they are treated the same way. About 20 percent of Merkel tumors are caused by UV exposure, and the other 80 percent are caused by the virus.

Nghiem: *Prior to 2008, no one knew there was a virus that causes this cancer. And there was a lot not known about the cancer in general. But this virus is incredibly common on our normal skin. We get it when we're children. It causes no problems that we're aware of, until usually 60 or 70 years after we get the virus. And then in 1 in 3,000*

people, over their lifetime, they will get this cancer caused by this virus.

While it's clear this virus causes many Merkel cell carcinomas, only a very small percentage of people who contract the virus end up developing this cancer.

There isn't a definitive reason why this small number of people end up developing cancer. But there are a few additional factors that seem to contribute. Merkel cell carcinoma predominantly affects older adults – the average age for a patient with this cancer is 74 years old. It's twice as likely to affect men. And it has some affinity for people who are immunosuppressed.

Nghiem: *A big reason why this cancer is not much more common is that the immune system has to be kind of not functioning at its top. And mostly that just means you need to be over the age of 60 or 70 or 80.*

And our immune system gets a little bit less robust as we get older. And that's what we think is the major cause. But if you have HIV or a profound immune suppression, you got a kidney transplant and you're taking immunosuppressive drugs, that increases your chance of getting this cancer by 10 to 50 fold.

However, most people don't have any problem with their immune system.

This brings us to diagnosis. If you have a lump somewhere on your body, how does a doctor figure out it's Merkel cell carcinoma?

First, they'll take a look at it. This part can be tricky because Merkel cell carcinoma is so rare. A dermatologist who isn't a specialist might only see a few of these tumors in their entire career. But they do look different from other, more

common, skin cancers, like melanoma, basal cell carcinoma or squamous cell carcinoma.

Nghiem: *Most melanomas are brown or black, and we kind of rely on that. They rarely break that rule, and you know, maybe multiple colors and brown and black kind of thing. Then squamous cell and basal cell- the basals may bleed very easily. They have prominent blood vessels in them. They're sort of translucent-looking. They're almost always on heavily sun damaged skin.*

Squamous cell carcinoma is usually red with scaliness and crustiness, perhaps. And a little bit more substance as compared to early pre-squamous cell, if you run your finger over it, it doesn't feel like there's a bump underneath. Once it turns into a squamous cell carcinoma, it feels more lumpy-bumpy, as well as often sort of crusty and scaly.

And Merkel cell carcinoma is variable. A good chunk of the time it's just a firm bump and the skin itself on top is totally normal. The most common colors for Merkel cell carcinoma are red and purple, and as the tumor gets a little bit bigger, it shows those colors more often.

Thakuria: *A lot of Merkel cells can present a little bit deeper, sort of under the skin, and those can be very hard to diagnose because they can look like benign things like cysts and lipomas.*

I don't want people to have the impression that cysts and lipomas are always Merkel cell carcinoma though, because 99.99% of the time, if it looks like a cyst, if it looks like a lipoma, it is a cyst or a lipoma.

So, you know, I'm a practicing general dermatologist also, and I see patients who come in and they go, 'and what's this lump?'

And so, you know, if I biopsied every cyst and lipoma, I'd probably keep our doors closed to patients who actually had bad skin cancers and needed to get in. So that's not the answer. But I do tell patients always, you know, if this lesion is not behaving the way that we're expecting, which is that it really doesn't change, you've got to call me.

Once your doctor identifies a tumor and does a biopsy, a diagnosis can be made. Merkel cell carcinoma has very distinct characteristics that a pathologist can recognize.

Thakuria: *And then your doctor would let you know about that diagnosis and talk to you about a treatment plan, or depending on that doctor's experience with Merkel cell carcinoma, they likely would be referring you to, you know, most likely an academic center, or a bigger center where they have some experience with Merkel cell carcinoma.*

This cancer requires unique care and attention. And it's important to have a team of specialists involved in treatment as soon as possible. This includes dermatologists, medical oncologists, radiation oncologists, and surgical oncologists. It's also crucial to work with people who have specific expertise in treating Merkel cell carcinoma.

Nghiem: *In the past, most institutions didn't have anybody focused on this cancer.*

It's now great if they've got somebody who focuses on, you know, many surgeons- 'Well, yeah, I'll cut out a Merkel!' That's fine. You know, but that doesn't mean they're taking care of the patient over time. And that's what you need, because this is a cancer that's got a 40 percent chance of recurring. It's very tricky at many stages. You need somebody, you need a team, really, that's kind of cohesive.

Dr. Nghiem and his team at the University of Washington are trying to bridge the gap between patients and the specialized

care they need. They run a website called merkelcell.org. This includes resources for patients, information about treatments, and a list of centers that specialize in Merkel cell carcinoma.

Nghiem: *So, we have identified a few dozen active centers around the United States and the world, where there [is] a team at that center that are saying, 'Yes, we have planted a flag. We care about Merkel cell carcinoma. We will take care of these patients. We will get them in quickly. This is a cancer that grows quickly and needs special multidisciplinary care.'*

And so that's something that you can't assume every cancer center or certainly, you know, small medical center has that expertise.

So you do need to do some regional travel, probably, to get- at least for one visit to some place that's going to advise you in a good way about what to do using multidisciplinary thinking.

Thakuria: *Merkel cell patients come to see our entire multidisciplinary Merkel cell carcinoma team. And they'll visit with every doctor. And what we do is we, you know, all meet the patient. We give our own assessment. And then we discuss and we have a multidisciplinary tumor board where we discuss every patient and come up with a really solid plan for that patient.*

Silk: *So I usually tell the patients, if they have a question about their skin, they can call the dermatologist. If they have a question about their surgery, they can call the surgeon. And if they have a question about the radiation therapy, they can call the radiation oncologist. If they don't know who to call, then they can always call me.*

(patient story)

Leon Igras: *My name is Leon Igras. I live in Scottsdale, Arizona. My age is 72 and the diagnosis that I've obtained from the Mayo Clinic is metastatic Merkel cell cancer.*

Because I live in Arizona, you know, there's a lot of sun exposure down here. I've been seeing a dermatologist for like, every six months to a year, they would do a body scan and they'd occasionally remove some little flaps or little things that they didn't think were cancer, but they'd remove them with liquid nitrogen. And I've had quite a few of those little things removed.

In 2021, I developed three bumps on the top of my head, and I'm kind of bald, so you can kind of see it, but the dermatologist actually did a mole surgery. He did three mole surgeries on the top of my head, probably in the space of six months. And I asked him, was that unusual? He said, well, sometimes he'll do like three to four, and then it kind of goes away.

But he sent it to the pathologist and it was squamous cell, which is a pretty common skin cancer. And he buttoned me up and, you know, everything was fine. I continued to see him every six months just to be checked out.

In July of 2022, I noticed like a swelling on my throat. It progressed very rapidly. So basically I went to see my primary care physician. He did an ultrasound and he noticed some lymph node engagement. He sent me to an ENT oncologist who did a needle biopsy and the needle biopsy indicated that it was a neuroendocrine tumor, might be Merkel cell, but it wasn't definitive.

So he basically got me scheduled for surgery. Took a while, but I went into surgery right after Labor Day in September of 2022. And at the same time he referred me to a cancer center in Phoenix.

They're kind of a generic— they do a lot of oncology, see a lot of different kinds of cancer types. And I started seeing an oncologist. She basically prescribed radiation therapy, which is six weeks of radiation to the side of my face, and then the throat, and then also four times three sets of chemo.

I would have to— I'd do the chemo and then my blood counts wouldn't come back. So, she would do the chemo whenever my blood counts would return.

This all started in October. When I found that I had a neuroendocrine tumor, I did call, you know, the Neuroendocrine Tumor Research Foundation and went into your website and I found that the Mayo Clinic in Phoenix is what was, MD Anderson Danner Hospital, you know, kind of had specialists in this. So I contacted Mayo, I'm closer to them, and it took us a while to get into Mayo, but they accepted me as a patient.

So I went to see a neuroendocrine tumor specialist at the end of December. And he pretty much told me that Mayo had retyped the tumor and that two Mayo pathologists had determined it was Merkel cell cancer. It wasn't just a generic neuroendocrine cancer. It was a Merkel cell. And he basically said that the treatment for this, we wouldn't have you do the fourth round of chemo. So he pulled me out of the fourth round of chemo. I transferred to Mayo Clinic in January of 2023.

Where I am with Mayo is they're basically monitoring me. I do see a Mayo oncologist who's a neuroendocrine tumor specialist. And then I also see a Mayo dermatologist. Every six months I'm examined there. So that's kind of, where I am.

What I would recommend, if people have a possibility of Merkel cell, they should get a second opinion of the cancer type.

No one ever mentioned Merkel cell until, you know, I met with the Mayo surgeon. His theory was that it manifested itself earlier, but it had been mistyped and wasn't diagnosed as Merkel cell.

There are three main kinds of treatment for Merkel cell carcinoma. The first is surgery, which is done whenever possible to remove the primary tumor. The second is radiation, which often accompanies surgery. And the third is immunotherapy, where a patient's own immune system is harnessed to fight tumor growth. This last option is reserved for more advanced cases.

To determine what kind of treatment is necessary, one of the first things your care team will do after the initial diagnosis is a PET/CT scan. This is important because of how rapidly Merkel cell carcinoma can spread to nearby lymph nodes and throughout the body.

Nghiem: *There is no Merkel cell carcinoma, no matter how small, that doesn't have at least a 5 or 10 percent chance of having already jumped someplace else. So we get a PET/CT scan and that will upstage patients in about one in seven or eight patients. We will suddenly realize this has jumped to lymph nodes or to, you know, an organ elsewhere in the body. And our big problem is not the little bump on the skin.*

Silk: *Often more than one type of treatment modality is needed because it is so aggressive. Merkel cell can spread through the skin, it can spread through the lymph node channels, or it can spread through the blood.*

So the first part of the best treatment is figuring out the correct diagnosis and the correct stage, and the treatment follows from that.

Thakuria: *If imaging didn't show any cancer anywhere else besides the one spot on their skin, we would then recommend for the patient to have something called a sentinel lymph node biopsy, which is a really neat procedure where they inject a little bit of dye and inject a little bit of a radioactive tracer into the skin. And then that gets taken up, to the draining lymph node basin. And instead of showing you all the lymph nodes in that basin, it will highlight the one or two or three or maybe four lymph nodes that are draining that little piece of skin.*

And so that way, the doctor, the surgeon can selectively pluck out just a few lymph nodes, look under the microscope and tell us whether or not there is microscopic spread of disease to the lymph node.

And that's a very common thing, unfortunately, that does happen in Merkel cell. So I always counsel patients when I meet them before they have this procedure that there's probably about a 25 percent chance on average that test will be positive.

Silk: *For example, if the Merkel cell carcinoma is located on the patient's right cheek, it's not uncommon for them to have metastases located in the lymph nodes in front of their right ear or in their right neck. This means they have stage 3 Merkel cell carcinoma, specifically stage 3b. This requires very aggressive treatment. So patients typically have surgery to remove these areas, or in some cases, it's decided by the multidisciplinary team of doctors that radiation therapy is in their best interest.*

Thakuria: *Radiation is a great treatment for Merkel cell carcinoma. This is an exquisitely sensitive, uh, radio*

sensitive cancer. And so we see sometimes even big tumors that are inoperable, the patients can't get surgery because they're not healthy enough- we have seen tumors just shrink away with radiation alone.

So in our center, and this is a difference maybe from center to center in our center, we tend to use a lot of radiation. And we find that can often avoid big complicated surgeries that often have their own set of bad side effects for patients, and scarring and things like that, that we try to avoid with radiation.

The third line of treatment after surgery and radiation is immunotherapy. This activates the immune system to attack the cancer. The immunotherapy treatment used for Merkel cell carcinoma is known as checkpoint blockade therapy.

Here's how it works: the immune system includes T-cells, which are white blood cells that fight off disease. Their action is usually regulated by certain molecules, called PD-1 and PD-L1. This treatment blocks those molecules, which unleashes the T-cells to attack the cancer.

Thakuria: *The immunotherapy works by almost, you can think of it as like turning on a switch and saying, okay, 'Wake up T-cells. You go now fight that cancer!' And, it does a really great job in that, especially for Merkel cell carcinoma.*

So Merkel cell carcinoma, here's some great news in Merkel cell carcinoma: Merkel cell carcinoma is one of the most responsive cancers to immunotherapy.

So it has completely changed the landscape of how we treat patients, even how we counsel patients at the beginning. There's just- there's so much more hope because if you respond well to immunotherapy, then even with stage four

disease, you really may have disease that can be managed for years, maybe many years.

Nghiem: *It's an IV infusion given every few weeks. About a third of patients will have at least significant fatigue. Noticeable fatigue, I should say- most people, their lives are not messed up from fatigue, but they notice it. And about 10% of patients will have a significant autoimmune problem. Like their thyroid will be damaged, that's the single most common thing. So you need to, in that case, take thyroid medications after that.*

But some people will have things we have to watch for very carefully, like problems breathing, problems with their lungs, problems with their gut. And we know how to manage those things. We stop the drug, we give some prednisone and we can turn off that autoimmune problem in those cases.

So it's pretty effective. More than half of patients will have a really good response where the tumors have shrunk either a lot or totally. We sometimes see after one dose, the tumor is gone under the microscope. It's- it can be really fast.

Silk: *Cancer grows fast, but it can also shrink very fast. Often the patient has immune cells waiting in the tumor, but they're exhausted and they cannot attack and kill the tumor.*

And with the addition of immunotherapy, the T cells get the right signals that enable them to become reactivated. And kill their cancer cells. I've had patients call to report benefit in as little as a few days after their first treatment. It can be really remarkable and it's very rewarding to take care of patients who are lucky enough to have this kind of response.

Nghiem: *Other people, you know, need to take these medications for several years and it's a tricky, we don't know when to turn the medication off, take the medication off. In some patients they will have the cancer come back 6 or 12 or 18 months after we've turned the medication off and then we put them back on the medication and it works again.*

So there's a subset of people that seem to need it for a long time. Others do well after only a few treatments and we have to stop it because they have some kind of side effect and some of them stay in response for years. So it's a tricky thing, much like the immune system in general, it's got a little bit of a mind of its own.

Merkel cell carcinoma isn't just rare and aggressive – it also has a tendency to come back after treatment. This cancer has a 40% recurrence rate, which is much higher than other skin cancers.

Because of this, patients are carefully monitored. There are two kinds of tests that are commonly used.

Nghiem: *One is looking at antibodies to the Merkel polyomavirus, the parts of the virus that actually make the cancer cell grow. Those parts of the virus have to be in the tumors that are driven by the virus.*

So the immune system sees this part of the virus that's causing the cancer to grow and those antibodies go up when the cancer grows. And when we cut the cancer out, they fall back down to zilch. And when they start going up again, we know the cancer is recurring in those patients. So that is a test that our team in Seattle developed starting in 2010.

The trick is though that only works for about half of patients that actually make those antibodies and that the cancer is caused by the virus. For the other patients that

don't make the antibodies, [and] they have the cancer caused by sunlight, we're now using circulating tumor DNA, which is a highly customized, highly sophisticated test in which a given patient's Merkel tumor is fully sequenced.

The DNA is fully sequenced. We look at the DNA in the normal blood cells and we make a comparison and find the specific mutations that Joe has in his Merkel. And then the company makes a set of DNA tests specific for Joe that says, 'Is this mutation present? Is that mutation present?' There's 16 of them and it turns out that is a fantastic way to find even tiny amounts of the cancer in the body.

(patient story)

Stewart Landers: *My name is Stewart Landers. I'm 67 years old. I live in Boston, Massachusetts, and I am living with Merkel cell carcinoma.*

Because I'm so fair-skinned, I started seeing a dermatologist routinely in my forties, and I've had a number of basal cells and squamous cells, and actually one melanoma that was caught very early, because my husband cuts my hair, and he saw it, so that was really fortunate.

But about two and a half years ago, actually three years ago, I had just a small little red bubble on my cheek. And I see two dermatologists, six months apart. So I saw one of them and he looked at it and froze it and it disappeared. Uh, but it came back, uh, a few, a couple of months later. And then in January of 2021, I saw my other dermatologist and he biopsied it.

And in February 2021, he told me that it came back as something called Merkel Cell Carcinoma, which I've never heard of before in my life. And I was both glad that it was now diagnosed. But when you go online and start reading about Merkel cell, you learn that it's more aggressive than

melanoma and has fewer treatments and a higher mortality rate.

The treatment was to, surgically, to go with what they call a wide excision, which I guess takes a fairly good chunk of the skin away. And then of course they sew it back up, but to try and make sure they've gotten all of it. They also, at the same time, inject some kind of dye to see what lymph nodes that particular lesion drains to.

And they found it drained to three lymph nodes in my neck and they excised those- they took those three lymph nodes out of my neck, and one of them was cancerous. The fact that it had spread to my lymph node made me a stage 3A, and it also meant that they followed up with radiation to my entire neck and my right cheek.

That was completed at the end of May 2021. And the hope was that they got it all.

I was fine until March or April of 2022. There is a blood test that measures Merkel tumor cells in my blood. They started that in the fall of 2021. My readings were very low. They started to tick up in the end of winter of 2022. And so they did another PET scan, and they discovered that I now had Merkel cell tumors on my liver. And that was really scary.

I'd asked one of my doctors early on how Merkel's actually kills you, and what they said was it attacks a vital organ. So I was really, needless to say, upset and concerned.

I started on that immune modulator, Keytruda is the trade name, Pembrolizumab is the generic name, and was on that through November of 2022. The tumors were still forming on my liver, although some had gone away, which was a little bit unusual. My doctor said, usually, it kind of doesn't work at all or works completely.

But because some of the existing tumors were still growing, she took me off of the Keytruda and put me on two off label drugs. Unfortunately, there's not necessarily reimbursement for that, and they're very expensive. But I've been on that now since December of 2022, and it's been somewhat similar to what happened on the Keytruda. Some of the tumors went away, but new ones grew. What we were able to do in April of this year was some targeted radiation that we hoped would get rid of kind of the last tumor that had been persisting on the liver.

It did. The treatment's effective, but two new ones came onto the liver- grew. And in July they removed those two, and again, that's effective, and I just had a scan, and there are no new liver tumors, so I've got a little bit of good news.

When people look online and learn about the disease, it can be very disheartening, but there really are.

A lot of people who are doing very well, if you catch it early, you may just be able to may just be a skin spot. And if you are able to excise it, it may not spread. But even if it does spread, there are many more treatments than I initially thought.

So even if it spreads, as I've been describing, to my liver, there are things that can be done that I wasn't aware of.

There are a handful of developments for treatment in the works. For example, right now immunotherapy is only FDA approved for patients who have stage 4 disease. That means they have distant and widespread metastases, or many metastases in one area of the body, but are not good candidates for surgery or radiation therapy. Researchers are seeking to change that.

Silk: *Currently we are conducting two clinical trials to look at whether we should move immunotherapy into earlier stage disease. So patients who have stage three disease typically are treated with surgery and/or radiation therapy and then they go into surveillance and follow up mode. But we wondered whether immunotherapy early, when they might not have cancer, or if they do have cancer, it's just a few cells, whether that makes sense and whether it's worth the potential cost and side effects.*

So there are two studies that are nearly complete. And one day we should have the answer to the question of whether immunotherapy should be used for stage three disease, but right now it's considered investigational.

One of the main challenges in making advancements in treatment is that clinical trials are hard to do with such a rare cancer. Fewer than 3,000 patients are diagnosed every year, so there aren't a lot of cases to work with

Silk: *In Merkel cell carcinoma, a big trial is considered 100 patients, where in a common cancer like lung cancer [or] breast cancer, that would be considered tiny. The FDA has some understanding of rare cancers and makes certain modifications when it comes to approving drugs in this rare cancer, but certainly not being able to have a control group in every study makes it hard to demonstrate that drugs are really working the way we think they are.*

Nghiem: *How do you do a clinical trial on it? Well, one way to do it is: this was such an ignored cancer in the past that when you compare the old standard with the new agent, you get this result that is so black and white, you don't need thousands or even hundreds of patients to make a clear conclusion.*

The chance that a patient will respond to immunotherapy in a prolonged way, as compared to chemotherapy, [which was]

the standard prior to 2017, is now tenfold higher. So that kind of difference is not something you need a thousand patients to be able to see. And that's what actually the FDA told us. They said, you know, you probably don't have to do a randomized study if you're going to have some huge difference, like a fourfold difference. That's what they were saying. And we ended up seeing a tenfold difference. So that was really gratifying in multiple studies that have shown these immunotherapy agents are enormously more effective than chemotherapy.

Silk: *Broadly speaking, all of the clinical trials that we're doing are tending to build on immunotherapy. One thing that's very exciting in Merkel cell carcinoma these days is we are thinking about not only using immunotherapy in patients with earlier stage [disease], but actually changing when we give it to the patients.*

Typically, the initial treatment has been surgery and radiation, but we're starting to think about patients who come in with pretty advanced stage three disease and whether they might benefit from getting some immunotherapy as their first treatment. We call this neoadjuvant or preoperative, but what it means is that patients get a few doses of immunotherapy in preparation for treatment with surgery or radiation therapy.

We think this can have a number of benefits. It is potentially something that can reduce the burden of cancer so that the surgery or the radiation has a lighter lift. And secondly, it can turn on the patient's immune response against their cancer cells so that even after they have their curative intent treatment, their body still remembers what their cancer looks like. And we think that could potentially prevent relapse in the future. But we certainly need to study this in more detail because there's very little out there in the literature right now.

For all the research yet to be done, diagnosis and treatment of Merkel cell carcinoma has come a long way in a relatively short period of time. And even though it is a rare and aggressive cancer, there is excellent care and support for patients -- and that will only continue to improve.

Nghiem: *You know, when I was a dermatology resident, I had a 90 year old guy who had a bump on his lip and I did a biopsy and that was a Merkel cell carcinoma. And that was in the 1990s. And, you know, then a professor forced me to write a chapter on the topic, and I wasn't interested, but then patients started coming from all over the place. And then I was a scientist interested in immunology and cancer biology, and then this thing turned out to be phenomenally interesting.*

So, yes, it is a really big part of what I do now in research and clinical care, and it's turned out- I mean, the virus came more than a decade after I was studying the cancer. So it's changed so much over these years, and we have interesting ways to track the cancer by watching the antibodies in the blood to the virus.

And now, so-called circulating tumor DNA is really effective at tracking whether the cancer is coming back or not. So it has been a real passion. Uh, and it's been incredibly gratifying to watch the field grow- [the] number of publications, the number of people interested, the number of centers around the country and the world that realize this cancer is not just melanoma. It really needs to be treated and understood differently.

And watching the progress in how we do surgery, how we do radiation, how we do systemic therapy, how we surveil the patient with blood studies now more than scans, it's just been an amazing journey and a real privilege to be able to

collaborate with and think with people who are changing the way that we manage this and other cancers.

Thakuria: *I think it is important to know that this is a dangerous cancer. It can be potentially very aggressive. And patients will hear that ad nauseam actually, like everybody will say it to them. They'll be terrified by the time they walk through our doors.*

But I do try to be transparent about it because occasionally you get a patient who is not aware of that. And I think it is important for patients to be able to make good decisions, knowing the facts.

However, that's not the main takeaway.

I think the main takeaway that patients should go home with is that they're not in a hopeless situation. And we have a lot of great therapies for Merkel cell now. And, you know, we see patients living long, happy, productive lives.

So I think it's very important to know that, you know, you're not in a hopeless situation. And that's what I would want any patient listening to hear and, and to believe: that there's a lot of great options for treatment of this cancer.

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

Our Production Partner for this series is CitizenRacecar.

This episode was Written and Produced by Anna Van Dine; Post-Production by José Miguel Baez; Production Manager, Gabriela Montequin; Executive Producer, David Hoffman

It was made possible by the generous support of Ipsen; Novartis; and TerSera Therapeutics.

Special thanks to everyone we interviewed for this episode. We are grateful for your expertise.

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