Episode 37:
Unusual NENs
Transcript

If you're new to NETWise, we highly recommend you go back and listen to the first episode in this series. It goes over the basics of neuroendocrine tumors and how they're treated. And you can find a whole library of episodes on different topics at netrf.org/podcast, where you'll also find infographics and videos that expand on this material.

If you have a story to tell about your own NET journey, please email us and let us know – podcast@netrf.org

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There's a common story told about neuroendocrine tumors. It goes like this: after a period of misdiagnosis, or completely by accident, a person discovers they have a NET. They learn that these tumors usually arise in the small intestine, the lungs, or the pancreas, and tend to metastasize to the liver. Their doctors explain that these tumors are slow-growing and that there are several treatment options. As a result, many patients are able to treat their cancer like a chronic condition.

This story is told because for a majority of NET patients, it's true. But this disease is far more complicated than that. Neuroendocrine neoplasms can arise in many locations throughout the body; they can grow rapidly; and they can occur under unique circumstances.

There are many patients whose NET journeys don't look anything like the story that is so often told. This episode is devoted to some of those more uncommon situations.

You're listening to NETWise. I'm Jessica Thomas, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

In each episode of this podcast, we share expert information and patient perspectives to help neuroendocrine cancer patients and caregivers navigate their journeys.

In today's episode, we're going to talk through some of the more uncommon locations – and situations – where neuroendocrine neoplasms arise.

Welcome.

In case you missed our last episode, a quick reminder: you're going to hear us use the term "neuroendocrine neoplasms," or "NENs," when we're talking about BOTH neuroendocrine tumors AND neuroendocrine carcinomas. It's an umbrella term that encompasses both types of tumors.

We're going to begin by talking about uncommon locations. With a NEN, it's important for your doctors to know where your

primary site is - this is the place in the body where the tumor first appeared.

Will Pegna is a GI medical oncologist and Assistant Professor of Medicine at Oregon Health and Science University in Portland.

> ***Pegna:*** *Really, finding the primary site for neuroendocrine tumors is really important because we know that different sites respond differently to different treatments.*

Like we mentioned earlier, there are a handful of places where these tumors are typically found.

Thor Halfdanarson is a medical oncologist and a professor of Oncology at the Mayo Clinic in Rochester, Minnesota

> ***Halfdanarson:*** *If you look at the- sort of the epidemiology and the trends in the U.S., the most common locations would be the small intestines, pancreas, lungs, stomach, rectum, and appendix.*

These parts of the body are where more than 75% of NETs arise. Which makes sense – these are places that have a high density of neuroendocrine cells. But these cells are also located in most of our other organs – and any one of those cells could develop a glitch in its DNA that causes it to become cancerous.

Halfdanarson: *You can really have a neuroendocrine tumor arise anywhere in the body.*

This means that there are a number of less common locations that NET specialists sometimes see.

Halfdanarson: *You can have them, for example, in the thymus gland in your chest, you can have tumors in the bile ducts, you can have them in the female organs, so in the uterus and the cervix and the fallopian tubes.*

One study identified 13 NETs in rare locations: breast, ovary, endometrium, vulva, uterine cervix, extrahepatic biliary tract, kidney, sinonasal tract, and thymus.

Overall, these and other uncommon locations account for fewer than 1/5th of all NET diagnoses.

We should also note that sometimes, doctors discover that a more typical NET primary has metastasized to what might seem like a unique location. It's important to understand that these metastases are not the same thing as uncommon primary sites.

Halfdanarson: *So, small bowel neuroendocrine tumors, for some strange reason, seem to metastasize behind the eyes to the orbital muscles. And it's a very unique, and not uncommon at all site of metastasis. Same thing with soft tissue under the skin, the breast tissue and – like unusual metastases to the heart, we're actually picking*

up more and more metastases to the heart. They don't start in the heart, but they go there.

And then one that comes up a lot of times, is people say, well, I have this person with a primary liver neuroendocrine tumor. Those are probably extremely rare, and I would think that most of them are metastases from somewhere else. But that said, sometimes you just don't find a primary tumor, and we have to conclude that this is a primary liver neuroendocrine tumor.

Now that we've talked about location, let's move on to speed.

How quickly a tumor grows depends on what kind of NEN it is. NETs tend to grow slowly, and because they make up the majority of neuroendocrine neoplasms, we often talk about this slow growth.

Neuroendocrine carcinomas, meanwhile, are a far more aggressive form of cancer, with a more grim prognosis.

And there's a notable overlap between NECs and uncommon primaries:

Halfdanarson: *A lot of these sort of more rare neuroendocrine tumors are neuroendocrine carcinomas. So for example, in the head and neck region, we can have a poorly differentiated aggressive neuroendocrine carcinoma. In the lower esophagus, we can see them, in the colon. Same thing with the female organs, especially*

the cervix – typically high grade, poorly differentiated neuroendocrine carcinomas.

NECs are somewhat common in the lung region, but outside of that, they are considered rare. This means that if you have an aggressive NEC in almost any other location, you are dealing with an uncommon situation.

Bill: *My name is Bill Thach. I am located in Houston, Texas.*

Back in November of 2018, I had blood in my stool, which was fairly recurrent. So I went to go see my PCP and he basically said it was hemorrhoids, and when I pushed against him a little bit, he had a CT scan ordered, and I did that. But a part of me feels that he didn't really read my CT scan, and just basically did it to please me.

So then I thought it was something wrong with the autoimmune issue that I had, spondyloarthritis, where I was like, okay, I'm going to see my rheumatologist to see if that is part of the issue.

So when I went to see my rheumatologist, he said that this had nothing to do with my spondyloarthritis. So he then referred me over to a gastroenterologist, and then we had scheduled a colonoscopy. And then that's when I discovered my tumor.

We had a six centimeter tumor in my rectum and a pathology report was then sent to MD Anderson. And that's

where I got diagnosed with neuroendocrine carcinoma, as a stage three rectal primary, and then I later advanced to a stage four.

It was somewhat of a shock and a surprise, just because I thought I was a fairly healthy person. I always exercised, I ate pretty healthy, and it somewhat blindsided me. And when I started researching the disease, I was like, okay, this is a very rare cancer.

And then at the same time, there was hardly any information on neuroendocrine carcinoma. So I was like, okay, I need to find a specialist. Because as each day passed, I really did feel like I was dying, with the tumor growing so fast inside me.

So within the realm of neuroendocrine cancer a majority of the patients have NET, which is a neuroendocrine tumor. So this falls in between grade one or grade two, which is a slower growing tumor. Whereas with NEC, which is a grade three, it's a more rapidly progressive cancer that is more aggressive.

And then at the same time, the outcomes for these patients are fairly grim, where I've seen some NET patients live upwards to 40, 50 years, whereas a NEC patient, a lot of us are lucky to live past two years with our diagnosis.

The other thing is that the majority of the treatments out there are for NET patients. So, there's an unmet medical need for the NEC patients out there.

I was diagnosed back at the age of 33. I am 38 now. I've been through a pretty good amount of different treatments, Ranging from chemotherapy, radiation, surgery, ablations, targeted therapy and immunotherapy. The one thing that did keep me stable was targeted therapy. And I have also been through a pretty monster surgery where my rectum, my prostate, my bladder, seminal vesicles, my liver, and then we did reconstruction on my abdomen and pelvis was done all in one go. And then I also had liver ablation procedure right after that.

So the surgery was performed on January 20th, 2021, so it's been about three years and it's been fairly successful. Going into the surgery, my surgeon told me that I have a 99 percent chance of having recurrence, which I knew, but the main thought in my head was I just want as much of this cancer out of my body. So I could basically start clean and then be ready for the next time it pops its head up.

So about six months after I had my cancer present itself again in my liver. As of right now, I'm on my third clinical trial that's using a target therapy drug. We're currently in the second cycle, and I will actually be getting a CT scan tomorrow. So, after the CT scan

tomorrow and another, in about a week, we'll know if the treatment's working.

Like we just heard in Bill's story, discovering and diagnosing neuroendocrine neoplasms of any kind can be a long, frustrating process. There are many different ways someone might figure out they have a NEN -- and it's another thing that can be affected by a tumor's location. So how might an uncommon NEN be diagnosed?

Halfdanarson: *Sometimes it's because of what I call, like, a mechanical complication of a, let's say, blockage of the bile duct, because there's a neuroendocrine tumor in the bile duct or in the gallbladder.*

This can cause symptoms like jaundice, or darkened urine, that lead to testing that shows tumors.

Symptoms might also be caused by metastases that have spread to other parts of the body, similarly leading to testing.

Other times, a person might notice a lump on their skin and bring it to the attention of their doctor.

Halfdanarson: *And sometimes they are just sort of incidentally found. Someone comes in with, let's say a kidney stone or slips on the ice in the winter, goes to the emergency room, has a CT scan just to make sure that there are no internal injuries. And now there's a neuroendocrine tumor that was found that no one really knew of and it caused no symptoms at all.*

Since the process of diagnosis can vary so much from person to person and from tumor to tumor, let's take one uncommon primary site as a case study.

Let's imagine someone discovers they have a NET primary in their breast. How does that play out?

> ***Pegna:*** *It would probably be similar to so many other breast cancers, incidentally found on a mammogram, or perhaps a lump that was sort of noticed, and for which they underwent biopsy.*

The biopsy reveals that this is not typical breast cancer – it's a whole other kind of cancer, one the patient may never have heard of before.

The first and most important thing to do is to find a specialized, multidisciplinary team to carry out an evaluation.

A breast NET needs to be looked at with specific tools. This is because a neuroendocrine tumor, no matter where it arises, is still going to be a neuroendocrine tumor.

A NET in the breast will have more in common with a NET in the small intestine than it will with typical breast cancer.

> ***Pegna:*** *With neuroendocrine tumors, and in this case as well, it always has to be a very multidisciplinary approach to the care, regardless what the primary site is.*

Once the tumor has been diagnosed as neuroendocrine, there's imaging to do. This imaging would be very different from what would be done with a new diagnosis of a more standard breast cancer.

> ***Pegna:*** *But would involve cross-sectional imaging and multi-phasic imaging of the abdomen, specifically the liver, because the liver is really the area of concern for neuroendocrine tumors.*
>
> *DOTATATE imaging is also a critical piece and a difference here.*

Imaging with Gallium-68 or Copper-64 DOTATATE will help determine whether the tumor has somatostatin receptors, which would open up the use of some kinds of NET-specific treatments, such as somatostatin analogs and PRRT.

> ***Pegna:*** *And then when we start talking about treatment options, I mean, just very different than the treatment options that would be offered for breast cancer. We consider tumor resection, even if it's not localized, even if it's spread, we consider both primary tumor resection, resection of metastases, debulking of disease as much as possible. And it's consideration of targeting the somatostatin receptor, PRRT and others.*
>
> *All these things are sort of not approaches that would be done for almost any other breast cancer in that situation.*

All of these differences are due to the fact that no matter where a NEN arises, it's still neuroendocrine cancer. There are specialized tools we have to diagnose and treat NENs, and they are different from what might be used for organ-specific tumors.

But before we get into more detail about treatment, there's one more uncommon situation we want to cover. We've talked about various locations of primary sites, and the differences in growth speed that set some NENs apart.

But sometimes, a patient finds themself in a highly surprising situation: they have a non-neuroendocrine cancer, and over time, it begins to take on NEN-like aspects. In other words, one kind of cancer can begin to turn *into* neuroendocrine cancer, causing hybrid tumors. This is a very unusual situation, but it can occur.

> ***Pegna:*** *We see, not infrequently, patients who have been treated for a long time for an adenocarcinoma – the classic one is like prostate cancer – that they can develop these neuroendocrine carcinomas.*
>
> *Now, the origin of these is kind of poorly understood, but it seems to be that the neuroendocrine carcinoma, it's a little bit of a base cell type that these tumors, over a longer period of time can, can become neuroendocrine carcinoma or neuroendocrine carcinoma-like.*

Diagnosis for this involves biopsy of an existing tumor, which is already being treated and monitored.

We recently spoke with two prostate cancer patients going through this experience:

> ***Amit:*** *My name is Amit Gattani. I live in Northern California. And, my diagnosis started in November of 2018, and it was adenocarcinoma of prostate. So basically a prostate cancer diagnosis.*
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> *Right from the beginning, I was advised that I have a fairly aggressive kind of prostate cancer and the life expectancy, or at least, uh, what your standard of care medical system tries to kind of establish to manage expectations, was like 24 months would be a good run.*
>
> *So here I am five and a half years later or five and a quarter years later. So I'm still trying to figure things out and continue to figure things out.*
>
> *None of the standard of care treatments that I have done – and I'm like, I don't know, 9th or 10th round of kind of treatments, at this point – have been able to contain the disease. So the disease burden and load has continuously been growing.*
>
> *And about a year back, one of the biopsy revealed that 20 percent of my cancer is behaving like a neuroendocrine cancer. And that was in February or March of 2023.*

I had a similar opportunity to get tissue in August of 2023. And that showed that the neuroendocrine component of my cancer had moved from 20% to 35%.

So about 10 to 15 percent of prostate cancer patients like me tend to have this. So it's, it's not common, but it's not like I was one in a million but, given the layers of, you know, difficult things that I have been dealing with. You know, it was just like, Oh my God, one more thing now. So the prognosis of that is much, much harder and more challenging.

I mean, I worked with a panel of maybe six oncologists across the country and the body language and kind of feedback I got from everybody was like, this is… this is not going to be easy.

And my first reaction was okay, well, I hear you. What do we do about it now? And that was more surprising and shocking that: we don't know what to do. This is the type of stuff that is still very niche. We haven't figured out how to, how to monitor it, how to deal with it and how to treat it with reasonable expectations.

I mean, we'll treat it. We have some ideas and some tools. We'll treat it, but we really don't know where it goes.

Genetic sequencing tests have shown Brian McCloskey of San Diego that his prostate cancer was *also* beginning to exhibit neuroendocrine characteristics.

> ***Brian:*** *I was diagnosed in 2016 with prostate cancer. And so I've been on this journey for, you know, the better part of seven and a half years. And I'm one of the sort of fortunate stage four prostate cancer patients that have had extensive genetic proteomic transcriptomic sequencing to understand how my disease has changed over time.*

Like we said, cases like these are rare - but they do happen.

Regardless of where your NEN arises, or under what circumstances, the next step after diagnosis is determining what kind of treatment makes the most sense.

Treating an unusual tumor can be challenging, but it's something that experienced clinicians have done many times. No matter what your situation is, there are lots of potentially beneficial tools used to treat all kinds of NENs.

> ***Pegna:*** *Even if we don't understand much about that specific tumor, there's a lot of things that we can offer.*
>
> *There's a lot of information that we have from other neuroendocrine tumors that we can sort of extrapolate and bring into the treatment options for these tumors and experience that comes with dealing with resection of*

metastatic disease that might not be considered elsewhere.

This is another place where having a multidisciplinary team of specialists is important.

Pegna: *It's just so critical to have, like, a multidisciplinary approach to the care here because there are surgical considerations that have been widely studied and widely described to be of benefit for patients.*

There are interventional radiology options, embolizations, ablations, otherwise, systemic therapies that are given by our nuclear medicine team and nuclear medicine specialists specifically to review imaging and give guidance based upon this, and medical oncologists as well, as well as numerous others. So that piece is just so critical to neuroendocrine tumors, because this is not a disease for which there is 1 treatment, 1 size fits all.

By and large, treatment for an unusual NEN will follow the same process as more common NENs.

But it's still a puzzle for your care team to figure out -- when you have an unusual tumor, your treatment needs to be highly individualized.

One of the ways teams approach this is by forming a tumor board. This is a group of clinicians with different kinds of

expertise, who meet regularly to discuss the best treatment options for a patient.

> ***Halfdanarson:*** *There you have in the same room – which is now a virtual room – you have the surgeons, the pathologists, often like different radiologists. You have like a cross sectional body radiologist. You have a nuclear medicine specialist. And now the radiation oncologists. Everyone's sort of weighing in and coming up with a plan. So this is, I think ultimately beneficial to the patients. Well, number one, it saves them a lot of extra trips, and because we create the plan at tumor board and then we can set up a very targeted visit, with the people you really need to see. And then when it comes to like surgical therapy, I think experience really matters and, you want someone who does this often.*

Unusual tumors are often excluded from clinical trials, so there is a lack of clinically proven treatment options. That doesn't stop your care team from figuring out the best treatment for you, though it can sometimes cause issues with insurance coverage. But that's another thing your doctors can work to solve.

> ***Halfdanarson:*** *Most of the time we can settle that sometimes the, the insurance carriers, all they need is just a phone call, what we call a peer to peer call, where we just explain to them, yeah, you may never have heard of this, but it's actually, it makes perfect sense*

to do this, get this scan done and get this treatment approved.

And I'd say most of the time, they are willing to listen and say, yeah, that can make all make sense now.

And in the end, *all* NENs are different – no one tumor is exactly like another, even among common tumors. Your team will approach your situation with nuance and care, no matter what kind of tumor you have or where it's located.

Pegna: *Every patient has their own disease and every disease needs to be approached, within its own context and with its own specialized treatment plan. That's what we aim to do with every new neuroendocrine tumor patient is to see their disease wherever it may be coming from and develop a specialized treatment plan that makes sense for that specific patient and their specific disease.*

This special consideration is what makes a multidisciplinary team and experienced specialists so important. They have the expertise and the network to help them effectively treat YOUR tumor.

Halfdanarson: *I think I've seen a neuroendocrine tumor in every organ of the body except the placenta. And I've been doing this for 20 plus years. But as I often tell my trainees, my fellows and residents in the clinic, is that barely a week goes by in my clinic where I just look at something and say, I've never seen this before.*

And sometimes if it's like really uncommon and really strange, I send out this as sort of like a mini mass email to maybe five or 10 friends in the net world, then the U S and then Europe and say, this is what I saw in the clinic today, has anyone seen anything similar to this? And what did you do?

And the neuroendocrine community is amazing. So, I'd say within like four hours, like eight out of 10 have responded. So it just tells you how committed the neuroendocrinology community is to this. And that goes for my European colleagues as well.

It can be scary to discover you have an uncommon cancer – and it can be even scarier to learn you have an uncommon subtype of an uncommon cancer. But the NET community is here for you.

Whether you have a NET in your lung or a NEC in your colon, there are specialists who are committed to giving you the best care. And there are organizations like NETRF working to bring you useful information and fund research into cures. We are all here to help you navigate your cancer journey -- so you can live your best life even with a NET or NEC.

Bill Thach ["tut"], whose story we heard earlier, ran an ultramarathon this spring. It took him more than 8 hours, but he finished the 31-mile course. Whether you choose to run or walk, we are here to help you navigate your NET journey, too.

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Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education for the NET Research Foundation.

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

And a note: Amit Gattani, whose story we heard in this episode, recently passed away. We deeply appreciate that he shared his story with us.

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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