NETWise
A Podcast About Neuroendocrine Cancer

Episode 17:
Focus on Liver 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 Elyse Gellerman, from the Neuroendocrine Tumor Research Foundation.

In previous episodes, we've put the spotlight on some of the most important primary sites of NETs – the organs in the body where NETs originally appear, such as the small intestine, the pancreas, the lungs, and the adrenal glands. Today, we're going to focus on an organ that is almost never a NET primary site, but nevertheless is of crucial importance to many NET patients: the liver. Very often, the liver is the first and most significant site of NET metastasis, and

for many people, managing the disease in their liver becomes the most challenging part of their NET journey.

To understand why this is, we first need to learn a little bit about the liver and what it does. The liver is one of the largest internal organs – about the size of a football in an adult – and sits between your lungs and your stomach, taking up most of the upper right quarter of your abdomen. It's an often misunderstood organ, maybe because unlike the lungs or the heart or the stomach which basically do one thing each, the liver performs a really wide range of important functions. Here's Dr. Helen Te, a Hepatologist at the University of Chicago Medical Center and Dr. Mary Maluccio, a Surgical Oncologist and Medical Director of the New Orleans Louisiana Neuroendocrine Tumor Specialists Program:

> *Te: "The liver is an amazing organ. It covers a very wide plethora of functions that the body needs."*

> *Maluccio: "It's a lot more important than we think. How I explain it to patients is the liver makes stuff and it breaks stuff down. In making stuff, it makes some of the proteins that keep your fluid in balance, it works very closely with the kidney so that you don't get fluid overload.*

And here's Dr. Satya Das. He's a medical oncologist who co-leads the Neuroendocrine Tumor program at Vanderbilt University in Nashville:

> *Das: "One of the most common proteins that the liver is responsible for producing is albumin, the protein that actually*

keeps our blood in our blood vessels. The other thing that the liver can produce is hormones, for example, called thrombopoietin, which actually stimulates platelet growth."

Maluccio: "The breaking stuff down is equally as important. So that's where if you were to eat something from the intestine, the nutrition gets absorbed and it all gets funneled through the liver. And the metabolic function of the liver is to break it down into its component parts, and then deliver the good stuff to the body. And the bad stuff gets out either through your kidneys or through your intestinal tract."

The liver also breaks down toxins in the body – basically anything in the body that is not nutritious or otherwise useful.

Te: "It converts medications to active forms to allow the medications to work, or for those that are already in active forms it detoxifies those medicines to allow them to be safely eliminated from our body. It also removes toxins from the body, including ammonia which is a byproduct of our daily cell turnover. It has cells that are specific for filtering bacteria."

This wide range of important functions is probably the reason for some qualities that make the liver unique amongst our internal organs. First, it's loaded with redundancies, and so a remarkable amount of liver can be damaged or removed without it losing any of its ability to function.

Te: "We can technically lose about 70% of our liver and still manage to regenerate what has been lost and survive with the remaining 30%."

This is a good thing, because if we get beyond that 70% threshold, the effects of liver damage can be very serious.

Das: "Liver damage to the body can be quite catastrophic. You can get severe malnutrition as well as severe anasarca, which is just kind of fluid buildup throughout the body. You can develop low platelets due to the fact that it is not secreting thrombopoietin and perhaps most commonly you get accumulation of those toxins. So you can get toxic buildup of things like ammonia, which are normally excreted by the liver into the GI tract and other drugs can stick around in the system for longer creating side effects that stay for longer periods of time."

Another thing that makes the liver unique is that all of those different things going in and out make it the site of a really enormous amount of blood flow.

Das: "So the liver basically gets two-third of our body's blood supply."

And a lot of that blood comes to the liver from the GI tract, including many of the most common NET primary sites, so when cancer cells leave their original site and try to spread, the liver is often the first place they end up.

> *Maluccio: "Because the drainage is all through the portal vein, the vein that goes into the liver, and the liver is the site of first defense. Most GI cancers, the primary site of metastasis is the liver as the first site of defense."*

This is exacerbated by the fact that two things Neuroendocrine tumors crave are blood supply and metabolic energy, both of which are found in abundance in the liver, so when the blood carries tumor cells there, they find a very congenial environment to plant themselves and grow.

> *Das: "Cancer loves energy stores because it needs something to nourish itself. And so the liver by way of proximity, blood supply, and being a high nutrient location becomes a large likely landing spot for neuroendocrine tumor cells."*

All of this unfortunately means that when NETs do spread to the liver, which they very often do, those liver metastases can grow a lot. Very often these metastases are much larger and easier to discover than the primary tumor, and in a large percentage of NET patients, these metastases are discovered first, before it is even known where the primary tumor is located.

> *Das: "From my clinical experience, I would say it's over 50%. Many times, especially the way now imaging is done, particularly if a patient has a tumor in the small bowel it can be quite occult and not be seen on a CT or even MRI scan.*

I have seen some patients, and these have been documented in the literature as well, that neuroendocrine tumor patients only with liver disease and a primary tumor never can be found. Now we tend to believe that if it is a neuroendocrine tumor, it must have come from somewhere else just because there are not usually neuroendocrine cells in the liver. So in patients in whom we think about only the liver being the site of a neuroendocrine tumor, that the primary site may just be unknown. And so quite common that the liver is actually the presenting site for neuroendocrine tumor."

And liver damage can often be a more serious problem than the direct effects of the primary tumor. Sometimes quite serious indeed. Here's Dr. Xavier Keutgen, Director of the Neuroendocrine Tumor Center at the University of Chicago:

Keutgen: "The number one cause of death in neuroendocrine tumor patients is actually overwhelming liver tumor burden, meaning that the liver gets replaced by so much tumor that the liver can't function properly anymore."

Maluccio: "And that's why some of the treatments that we use for neuroendocrine tend to be focused on the liver. Many of the options whether surgical or nonsurgical have to do with how successful we are going to be with trying to decrease the tumor burden in the liver, whereby we will change that."

In order to treat these metastases, they of course first must be found and diagnosed. Sometimes extensive liver disease can be symptomatic and these symptoms can lead to diagnosis.

> *Das: "In the context of a high grade neuroendocrine carcinoma, those tend to be more symptomatic, and so folks with liver involvement from those types of diseases can feel liver fullness, what we call hepatomegaly just from metastatic stretching of the liver, nausea, right upper quadrant pain, and just generalized malaise."*

> *Maluccio: "And you'll have mental status changes, that can be a little bit like having a haze. We call it encephalopathy – when someone can be partly appropriate, but has sort of a glassiness or a distance to them that would suggest that they aren't really processing the information the same way."*

Liver damage can also cause build up of substances in the blood like bile and the bible-related protein bilirubin, which can cause digestive issues and visible symptoms:

> *Das: "Bilirubin in high enough levels is toxic to the liver, but then can also back up into the bloodstream, and that's what causes jaundice. So if we think about it, when bile is not excreted into the gut, bile is actually what causes the stool to get its color, brown color. So in folks that have, for example, obstructive jaundice due to extensive liver disease from their neuroendocrine tumor, the stool is what we call light colored and*

the bile actually backs up into the blood causing dark urine. So those are kind of the telltale signs of bilirubin buildup."

Because the liver is so resilient, though, a patient can have a really remarkable amount of liver disease without any obvious symptoms appearing at all. This means that liver tumors are often diagnosed incidentally – when a scan is being done for a totally unrelated reason.

Das: "Because the liver's a remarkable organ you can have 60, 70% involvement by a low grade endocrine tumor and still have no symptoms or even normal liver enzymes. And so many patients with neuroendocrine tumors are diagnosed based on an abdominal scan for another reason that happens to pick up metastases in the liver."

In the case of low-grade NETs, this means that someone can have liver metastases that grow for years or even decades before they are discovered, if they are discovered at all.

Das: "In patients with low volume disease who never get a scan or otherwise fine, I would be certain that certain patients live their whole lives without ever knowing that they have this disease."

And unfortunately, in cases where the primary tumor is discovered first, these metastases can hide in the liver – sometimes being discovered much later, after a person had thought they were cancer-free.

Once the tumors are found, it's really important to use tools like biopsies to confirm that we are dealing with liver metastases of a NET, rather than a different kind of liver cancer – these can look very similar on a scan, but have very different implications.

> *Das: "In oncology our saying is always tissue is the issue. So we always get a biopsy to prove what it is, because again, based on imaging alone sometimes it can be very difficult to tell what is what. We can think about it in two different ways. So primary liver cells that turn cancerous are turned into hepatocellular carcinoma or cholangiocarcinoma, whereas neuroendocrine tumor cells that seed the liver become neuroendocrine liver metastases. The treatment algorithm is very different."*

Because of the nature of NETs and the inherent resiliency of the liver, there are a lot of different treatment options for liver metastases. Finding the right one for you and your particular disease really becomes a question of getting to the right doctors and making sure they are considering all of the possibilities.

> *Das: "Multidisciplinary care is so relevant in this context, particularly with liver dominant disease, because there are so many different things that we can do."*

> *Keutgen: "They work together, they're not exclusive of one another and they should be used at the right time so that our patients can live as long as possible."*

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Patient story #1:

"My name is Cindy Lovelace. I'm 65 years old. I live in Nashville, Tennessee. I was diagnosed in 2011 with a pancreatic neuroendocrine tumor.

Well, when I had the pancreatic resection, which was very successful, they removed half my pancreas, lymph nodes, and my spleen for good measure, I was told by the surgeon you're good to go, you're cancer free. I lived with that for about six months. This was 2011, and in October of 2011 we were watching a new story that Steve Jobs had died. In that situation the reporter got it right, and explained that Steve Jobs had neuroendocrine cancer that started in his pancreas and went to his liver. Well, that got my attention. I literally Googled again, and for whatever reason, a doctor popped up first thing in my search that was in my city and it said neuroendocrine cancer center. I was going, what? Wow, there's a doctor right here in Nashville who deals with neuroendocrine tumors!

I went for a consult with him. He immediately told me, he said, well, your tumor in your pancreas was very small. He assured me that the surgery I had done was the correct surgery. And he said, but I'm a little suspicious because these tumors often metastasized to the liver. I said, well, what do we do? And ordered some scans. I had an MRI, the MRI showed really nothing remarkable in the liver. He had just started a clinical trial for the gallium scan. So I had the Gallium-68 scan and two tumors lit

up in my liver. So here I'd had an MRI that had showed nothing remarkable, I had the Gallium-68 really within a week or two later, and two tumors lit up in my liver.

At that time, the advice was let's watch them, they're very small. Let's see what happens because I don't want to be going in and doing surgery on a yearly basis or whatever. I don't want to overdo. And about a year went by and one of the tumors, which was closer to my heart in that particular lobe, he just became concerned about because of the way it was growing and also where it was. So I had that resection done, it was a very successful surgery. And since then I have had two more resections. One was a major de-bulking that I had in 2018, because these tumors had grown again and had continued to progress. After that last debulking of my liver, there were some very small specs, if you will, that were found in my mesentery and there was one that was found near my ovary. And so now we're dealing with something that's kind of jumped the liver, but the liver tumors are the main concern because your liver is an essential organ and that starts getting filled up with tumors, you have a problem.

So in 2019 I started looking at the possibility of a more systemic approach. And by this time what had come on the horizon was an opportunity to do this new treatment, Lutathera, or PRRT. And so I decided that this was the right approach for me because my overall health was good, I could tolerate the treatment. It was a possibility of kind of getting ahead of this and stopping the growth of these tumors in my liver, because they had continued to pop up. I had the treatment, I tolerated it really

well. I was given a year of stabilization and that was great, but the tumors began to grow again.

In 2021, just this past year, I took CAPTEM, which is an oral chemotherapy, for several months. I've had a really good response to that. My latest scans showed that I've had some shrinkage of some tumors and definitely stabilization in all of the tumors, so this is really great news. From what I understand, the CAPTEM could continue to work even though I'm not actively taking the treatment now. Of course I will continue to be monitored to see how I respond to this treatment. I'm still pretty healthy and functioning, and thankfully have had a good response to all of this treatment. Really, I'm very grateful that these opportunities are out there because when I was originally diagnosed in 2011, a lot of this was just coming into clinical trials. So here I am in 2022 with still more options on the horizon should my liver tumors continue to act up.

I think the other thing that really helped me was getting my mind right. I'm in a fight here for my life, and so I felt like I had to stay in the best physical shape that I could, because anything that is within my control I want to try to make that is as good as possible. So I do work hard at that. I've paid better attention to just my spiritual outlook, and I take time for that. That really helps me, I think, get through some things that can be pretty scary, pretty daunting."

With so many potential treatments for these metastases, which one is right for you? That's a complicated question, and one that a good care team will weigh very carefully.

> *Das: "It depends on several factors: so, first of all, what is the primary origin of the tumor? Are there sites of disease outside of the liver? Does the tumor express somatostatin receptors?*

Two of the most important considerations here are a tumor's differentiation and grade. The first of these is a description of the physical features of a particular tumor, made by a pathologist, that indicates how similar or different the tumor is from the healthy tissue surrounding it. The second is a measure of how quickly and aggressively a tumor is growing, based on the KI-67 index, which defines how many times a tumor's cells multiply over a particular period of time.

> *Maluccio: "What I tell patients is that this is one of the disease processes where grade and differentiation is probably actually more important than stage. So you can have stage 4 cancer but a very low-grade tumor and have a better prognosis than a higher-grade tumor, lower stage.*
>
> *And then once you have the grade and the differentiation, you're really looking at the pattern – the pattern of distribution in the liver. Are they individual sites of large tumors? Or do we have multiple, or innumerable, small tumors, because that's going*

to weigh in to which treatment is going to be most successful at managing that pattern of distribution."

As we've heard with other NETs, in cases where tumors are particularly low-grade, well-differentiated, small, and localized, the right way to proceed might be to watch and wait, because every treatment has potential side effects and complications.

Das: "A patient with a grade one neuroendocrine tumor could have had their disease for seven to ten years before diagnosis. And if they're not having any symptoms and their liver enzymes are in good shape, I think then we fall into the trap of over-treating. Because, what if someone's disease hasn't changed in three to five years, and now I'm putting them on a treatment, whether it's a monthly shot or putting them through a surgical intervention, and they didn't need it? And so, when we don't clearly have a timeframe in tow, and when we can't clearly remove all disease, I think sometimes waiting gives us that time to understand a patient's disease biology."

When it is time to treat a low-grade, well-differentiated NET in the liver, surgery is often a good option. It's important to note here that unlike with surgery on NET primary sites, even catching and removing these metastatic tumors early doesn't offer the opportunity of a cure. Once your NET has traveled to your liver, it will almost always continue to return.

Keutgen: "If the tumor has spread to the liver, you have about a 90% to 95% chance after we have operated that the tumor will come back at some point."

So the goal of surgery for low-grade NETs in the liver becomes long-term management – the phrase that's often used is "resetting the clock."

Keutgen: "Remember, these are slow growing tumors. It usually takes five to 10 years until you have a significant amount of liver metastases. And if we can take them all out or almost all out, we set you back five or 10 years and so you gain that time towards your lifespan."

This strategy opens up the option of "debulking" surgery, which generally doesn't make sense with faster-growing cancers. In this type of procedure, the liver metastases that can be safely removed are removed and those that can't are left in place. So long as a specific removal goal can be met, this can have significant benefits for a patient's prognosis.

Keutgen: "There's been many, many studies with thousands of patients that have shown that hepatic cytoreduction, so debulking of the liver tumor, makes a difference in terms of long term survival. So that means that we should probably consider resecting your liver tumors even if you have disease outside of the liver because there's other therapies, like PRT, and other systemic therapies that can take care of that part. But again,

the liver is important because the liver tumor burn is what's going to define how long you're going to live."

With these kinds of NETs, parenchymal-sparing resection can often be performed, in which the surgeon removes the tumor with very minimal damage to the surrounding liver tissue.

Maluccio: "In terms of neuroendocrine versus other types of metastasectomies, because you can stay much closer to the capsule, you can get it out and preserve a lot of the remaining structures and, therefore, you do not lose as much functioning liver.

Keep in mind that these are major surgeries, and come with all of the risks and complications that entails.

Maluccio: "It's a major open abdominal operation, general anesthesia, central lines in order to maintain some of the monitoring. It's probably five to seven days in the hospital. It can be probably a month to six weeks total recovery, but it's one of those where you sort of slowly, you may limp a little bit in the first seven to 10 days but once you sort of come around the corner it's just getting over a big operation. And the liver can bounce back very nicely so that six weeks later you can come down to normal liver function, go back. No eating issues, no this... It's you just really going back to your normal baseline function. But it's a big investment and it's probably a four to six-week recovery".

And surgery isn't an option for everyone – it depends very much on the number, position, and behavior of your particular tumors as well as your overall health.

> *Maluccio: "You have to ask yourself, am I going to meet my treatment goal? Am I going to be able to get out of the burden of disease that's going to make it worth this person investing in surgery?"*
>
> *Keutgen: "Livers with a lot of tumors or with a portal vein thrombosis, meaning clogging of the vessels that lead into your liver. Those are not good candidates to undergo surgery. When you have greater than 25%, some people say greater than 50%, of the liver replacement tumor, surgery's not going to help you because we can't reach the 70% or 90% debulking threshold that we need to do to improve your survival. When you have innumerable tiny metastases, we can't really help you either because they are usually too small for us to even find and properly remove. If you have carcinoid heart disease, you're not necessarily not a candidate for liver debulking, but we got to make sure that your heart gets fixed before we actually do the liver surgery. Obviously, if you're 95 years old and you have poor performance status, surgery's probably not the best option for you. And for high-grade tumors, that's also not a good option because they come by so quickly that surgery doesn't make a lot of sense."*

In cases where surgery isn't a good option, or where surgery has already been performed and it's time to move to something else, there

are other options. One of these are Interventional Radiology, which are often referred to as "liver-directed therapies". Here's Dr. Osman Ahmed, an Interventional Radiologist at the University of Chicago Medical Center:

> *Ahmed: "Interventional radiology, or IR, is a specialty where physicians like myself use imaging to perform minimally invasive procedures. And so while we conventionally think of radiologists as physicians who interpret images, we can actually use imaging to develop these techniques that guide wires and catheters into different parts of the body."*

There are several options here, which fall into two general categories – ablation and embolization. In ablations, individual tumors are attacked with a small, needle-like probe.

> *Ahmed: "In our ablation methods, the needle is the same, the concept is the same, the technique is the same, but what we do to the tumor can be different. So if we do RFA, or radio frequency ablation, or if we do microwave ablation, we are essentially burning the tumor. If we're doing cryoablation, we're actually freezing the tumor. And then there's other ways to treat tumors where we can actually electrocute tumors, and that's called IRE, or irreversible electroporation. But again, the concept is all the same, the needle is going into the tumor and is being plugged to a machine that will either burn, freeze or electrocute the tumor."*

The other family of IR treatments, embolizations, make use of a particular quality of the liver we heard about earlier – the fact that an enormous amount of blood flows through it. The blood flow to the liver comes from two sources, the hepatic artery and the portal vein. For whatever reason, NET tumors in the liver tend to take their blood supply from only one of these – the artery – while healthy liver tissue can get what it needs from either one. This opens the door to some interesting treatment options.

> *Ahmed: "Because the normal liver gets its blood supply from both the portal vein and the hepatic artery, and the majority of it is actually from the portal vein, we know that if we treat the hepatic artery, if we shut that hepatic artery down, the normal liver will still function but those tumors will die. And when we shut that blood supply down, that's called embolization."*

This is done by injecting what are essentially tiny beads into the artery where it connects to the liver, damming off the blood flow. This can be done with plain beads, which is called "bland embolization"; beads that give off cancer-killing medicine of some kind, which is called "chemoebolization"; or radioactive beads, which is called "radioembolization".

Your care team might suggest any of these options, again depending on the characteristics of your particular tumors.

> *Ahmed: "With ablation, we typically treat patients who have a few lesions as opposed to the transarterial therapies where we can blanket tumors with the beads. So if a patient only has a few*

lesions, we tend to do ablation. If they have a lot, we tend to do embolization type procedures."

The challenge of IR is that these techniques tend to be more damaging to the healthy tissue that surrounds the tumor. This means that the main qualification for IR is whether the liver, as a whole, can sustain this damage.

Ahmed: "The good news is that there's no amount of actual disease in the liver that limits IR treatment. The entire liver could be studded with tumors, but if the liver is actually functioning, the normal liver, then we know that we can still go ahead and treat. If, however, the liver function is bad, it doesn't matter how much tumor there is, we can't usually treat those patients."

Moving past these, there are also several medical interventions to choose from. None of these are shown to shrink the total tumor burden in your liver, but there is evidence that they can slow the rate of growth.

Das: "So for example, if we're dealing with a fast moving process in the liver with a patient with bulkier disease and a pancreatic neuroendocrine tumor primary, I might consider chemotherapy first, actually. The most active regimen in terms of response rate is capecitabine plus temozolomide. So I might use capecitabine and temozolomide for a finite period of time to debulk their disease systemically before giving them a break or thinking about maintenance therapy. If patients have a relatively slow moving disease and it's, for example, a small bowel primary,

and if their tumors are somatostatin receptor expressing, I might just think about octreotide or lanreotide to sort of quell their disease."

And as with many kinds of NETs, for liver metastases that are somatostatin receptor positive, PRRT is a recently-approved and very promising option. It seems that for some patients, it can be very effective for halting disease progression.

Das: "This has been a game changing therapy because we hadn't had a later line treatment that could freeze disease for such prolonged long periods of time. We're talking about years here, and also improving quality of life for patients in that same manner."

Maluccio: "What I like about PRRT, and how I explain it to patients, is that if you have somatostatin receptor avid disease, and you have it multifocal in a number of different areas, in particular a number of different organ systems, the idea that you can use a single treatment strategy to target multiple organs is definitely progress.

Das: And we have some data that actually suggests that perhaps earlier incorporation of PRRT to patients, when they actually have less bulk in the liver and other critical organs, may actually improve outcomes. So it depends a little bit on the primary tumor origin and also to what degree of liver involvement they have that would dictate my initial strategy."

And then in some NET patients with liver metastasis, liver transplant may also be considered.

> *Das: "This is a controversial one. I will say transplant in the context of liver metastases for a patient with a neuroendocrine tumor is a highly nuanced question and it should only be considered in very, very, very select cases, and that needs to be done through a multidisciplinary transplant center. I think the context in which it should be discussed is if, for example, a patient has liver only disease, the primary tumor removed, we've run out of systemic treatment options, the patient otherwise has many, many years left outside of this neuroendocrine tumor that's compromising the liver. That is the context in which it should be explored."*

> *Maluccio: "So there are distinct criteria because it's highly regulated in this country, but neuroendocrine is an indication for transplant. So it's going to be in the low grade, well differentiated. The people that have had a long disease interval, KI67 below a certain number, and you're starting to suffer from the consequences of the treatment of the disease and not the disease itself. That's where transplant comes in and is able to rectify that in a select group of patients and still have them then live considerably longer after that. It's not very many people that need that. It's not very many people that get there."*

And it's important to remember that for patients who might qualify for transplant, it is an extremely difficult and serious surgery,

with significant potential side-effects, so that burden has to be considered as well.

> *Das: "Yeah, huge ordeal with immunosuppressive medications that you have to be on your whole life. They can compromise things like kidney function, cardiac function, metabolism, so there's a whole host of things that go into that."*

And, even when successful, liver transplant in this context is yet another tool for setting back the clock on liver metastasis, not a way to stop them altogether.

> *Das: "The liver transplant itself is still not curative because we think that there are still neuroendocrine tumor cells circulating in the body and they will, again, take hold. But in that context, buying time is the biggest thing."*

Patient story #2:

> *"My name is Katherine Mueller, I'm 31 years old, and almost exactly three years ago I was diagnosed with a neuroendocrine tumor in my pancreas and with metastasis to the liver.*
>
> *Like many NET patients, it took a long time to be diagnosed. I had symptoms well before diagnosis, so it started out with... I mean, now I'm so open to talking about everything I don't really care, but it started out with diarrhea and of course, I just didn't really want to go to see the doctor about diarrhea so that*

was something I may have avoided for a couple months. But then once it was every day, I went to a doctor and because I have a history of IBS in my family they just automatically jumped to that so I was given some medication that didn't work but I got some blood work, that's what they kept ordering, and all my blood work was always normal.

And then I started having the acid reflux, and it got really bad to the point where I was throwing up at least twice a week and 'this is not normal'. So I went to a GI specialist and they finally did an endoscopy and colonoscopy, which didn't find anything. But for some reason she just had a nagging feeling and she did a gastrin test, and that blood test showed that it was sky high. So I think it's all about ordering the right tests because I kept getting all these panels of blood tests and everything was normal until that one. And then they did a sonogram and then a CT and an MRI and found that I had a lot of metastasis in my liver. It pretty much had already taken over it.

It wasn't real. I mean, it was crazy, especially when we just had the liver metastasis, they didn't know where the primary was from. I went to an oncologist at the hospital I work at, which he's amazing but he's not a NET specialist by any means, and he is trying to gently tell me that, "Since this is in your liver, it started somewhere else. It's not going to be curable." And I just couldn't fathom that, that something had gone that far without me knowing. How could that be? But I eventually was able to accept that once I thought maybe it had started in the liver... I just didn't understand much about this, and doing my

research and learning as much as I could really helped calm me down, even though I wasn't getting the news that I wanted. It helped me understand exactly what was going on inside my body and that was the biggest thing for me, just knowing, not just being unaware of what was happening.

We had to go searching for the primary. They sent me for an ultrasound guided endoscopy, and that's when they found the just tiny little one-centimeter tumor in my pancreas that had started this whole thing. And then that's what my husband and I were always concentrated on, we were like, "Can I get a whipple surgery? What can we do?" And my doctors always said, "We are not worried about that tumor. We're worried about your liver. We need to get that under control," because there was just so much of it that they were like, "That tumor is stable," which is so weird it stayed the same size the whole time I had it, just one of them, and it was the metastasis that was so aggressive.

But during my transplant, that was actually one of the reasons why they agreed to do it was because I didn't have any metastasis outside of my liver and they planned on removing my pancreas, the entire thing, during the surgery, which they did. So now I'm insulin independent diabetic but, I mean, we did what we had to do.

I have had a long road of treatments. So we immediately started out with the lanreotide shots, and that's basically, in my case, just for symptoms. We figured that isn't helping with the tumors.

I had a bland embolization, two chemo embolizations, two Y90 embolizations. I did cap 10, it's oral chemo, Afinitor, PRRT.

I've gone through the list. When I was first diagnosed, Dr. Kitaya wrote to me, she made me a piece of paper as my oncologist. She made me a piece of paper that was my toolbox and we just steadily checked each one off. And the most I've ever really gotten from any of these treatments is maybe one clear scan and then the next one, it's come back or it's grown or progressed.

They always told me that surgery was not an option. And then just this year I had a doctor that wanted to do a liver resection on me I think because I had gone through all of the regular treatments that they want to put you through first, I'd done them and nothing had really worked so he tried to do a liver resection. But once he opened me up, he realized it was too much, it was too extensive and it would've been more risky to do the surgery than just close me up. So that was a huge disappointment, waking up and being like, "So did you get it?" and nothing had really been done. And I still had this crazy recovery because I had this huge scar.

And then after that, I started really going into liver failure. My bilirubin was going up every time I got blood work, I was very yellow. And I found a doctor in New York, a surgeon, that took a chance on me and said that he would do a liver transplant. This was after I'd been given three weeks to live, which is a horrible thing to hear. Again, I just could not wrap my mind around how

that was possible. So he said he would take a chance on me, he did it. We're hoping that was my miracle... And it was my miracle because even though the cancer has come back, unfortunately, I had three weeks and now, in the amount of time that it's been, it's been like nine months since my transplant, we've gone to so many weddings, we've gone on vacations. We've done so many things with family so I had so much quality time that I hope the surgeons there know that it was a success for me, at least.

But unfortunately, yeah, I'm back on the train of trying to find different treatments. It's not great that... We kind of kicked the beehive I think. That's what they said that it could either hopefully they got it all and it would not come back or it might come back with vengeance, and that's what it's done.

Well, I had my first treatment of immunotherapy, so that's the next step.

Definitely don't take a passive role in your healthcare. Be your own advocate 100% and you won't have any regrets. Don't be afraid to change doctors and hurt somebody's feelings. So that was my whole thing, I was always like, "Well, they're okay. They're fine." No, we need the best. It's my life, so if there's a doctor that doesn't have great communication or they're just not doing everything I think possible they could then I'm on to researching the next one.

I'm so lucky that I found my oncologist. She is so responsive and she just explains everything to me bluntly but... She's not trying to hide anything or sugarcoat anything. So I would definitely say that, do all of your research, learn everything you can, and understand what's going on inside your body. Because I'm always boggled when I see these online support groups, when people don't really know anything about their disease, and you have to."

With a complicated disease like metastatic NETs, which has so many possible courses of treatments, the question often comes down to not so much *what* treatment to choose, but *when* each option is going to be deployed, and what the cumulative effects of these treatments are going to be, both positive and negative.

Maluccio: "That is most relevant for neuroendocrine because patients live a long time with the disease and therefore you have to use a lot of these treatments very judiciously. Each treatment is going to come with a certain amount of side effects for whatever response rates associated with that. None of the treatment options in neuroendocrine are mutually exclusive and they can be used in combination safely. You have to personalize the treatment to the disease that you've got, the symptoms that the patient has, the comorbid conditions, the other medical problems they have that may influence their ability to tolerate the treatment. So programs like this and educational programs and second opinions and things like that are that much more relevant

to neuroendocrine patients because each of us may look at the risk benefit ever so slightly differently."

These risk/benefit analyses can be complicated by any liver damage that might exist in a patient that is unrelated to their cancer. Unfortunately we live in a time when there is a near-epidemic of conditions like Non-alcoholic Fatty Liver Disease, which by some estimates affects as many as 100 Million people in the US alone. This can change the amount of healthy liver tissue a NET patient has in the first place, which can reduce the available treatment options.

Das: "The reserve of the liver is something that we rely on essentially, for both our treatments to be tolerated and also to give our patients time. So if a patient has underlying liver disease that absolutely influences both the therapies we can give, but also the course of a neuroendocrine tumor. So for example, we talked about earlier that all a patient needs is 25% to 30% of intrinsic liver function or liver cells to be present to function. But sometimes in the setting of cirrhosis, folks don't have that or folks are already at that limit. So you can imagine in patients with underlying liver cirrhosis or liver inflammation, the tipping point becomes much sooner. So those are patients that we really worry about because we worry about both our treatments being more toxic, but we also worry about lesser tumor burden causing more problems, underlying diseases. There's a big limitation for us."

Some good news for people wrestling with liver metastasis is that in addition to the myriad of treatment options currently available, there are a number of exciting possibilities for new treatments currently being studied.

> *Das: "It's really been a renaissance in sort of the drug development field in neuroendocrine tumors. We have novel tyrosine kinase inhibitors that are currently under regulatory review. One of these drugs is called "Sorafenib". This is actually a very exciting drug because it could be the first tyrosine kinase inhibitor approved for non-pancreatic neuroendocrine tumors, as well as pancreatic neuroendocrine tumor patients. So this is actually already garnered regulatory approval in China. It is being weighed by the FDA currently. Immunotherapy, there's a huge debate in the field as to whether immune therapy works in neuroendocrine tumors. And I think the shorter answer is that immunotherapy alone doesn't work but there are some very interesting combinations that are being looked at."*

New developments in PRRT also hold real promise for the future:

> *Maluccio: "The things that are coming down the pipe, like radioactive lead, that the data looks like it's going to be a higher response rate and lower toxicity, and that this may be the next generation of what will become multiple generations for people with metastatic neuroendocrine tumor. That's what I find most exciting."*

All-in-all, the most important thing you can do as a person with these tumors is to get to a care team that has real experience in dealing with metastatic NETs, and is exploring every option to help you live as long and as well as possible.

> *Das: "Liver involvement, more than any other site, is sort of a symphony between multi disciplines. So I think it is crucially important to get some multidisciplinary input from your NET team when dealing with liver metastases because there are so many things one can do given that each patient's case is very differently approached."*

A final note on this episode - between the time we recorded her interview and when this episode was published, Katherine Mueller passed away from complications of her disease. We are grateful that she wanted to share her story. This episode is dedicated to her memory.

Thanks for listening to NETWise. My name is Elyse Gellerman, and I'm CEO of the NET Research Foundation. This episode was written and produced by David Hoffman of CitizenRacecar; Production Manager, Gabriela Montequin *(mon-ta-KEEN)*. It was made possible by the generous support of Ipsen Biopharmaceuticals and Advanced Accelerator Applications, a Novartis Company. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. This is a production of the Neuroendocrine Tumor Research Foundation, where we're committed to improving the lives of patients, families,

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