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Welcome to NET Wise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. My name is Laran Hyder, from the Neuroendocrine Tumor Research Foundation.

There are two ways to treat cancer – direct treatments, which basically come down to finding individual tumors and removing them from the body, or systemic treatments, which introduce some kind of anti-cancer medicine into the bloodstream.

In this episode, we're going to address direct treatments, beginning with surgery. We'll start here, because if your NET can be surgically removed, it's usually the best possible course of treatment.

Here's Dr. Pam Kunz, Director of the Neuroendocrine Tumor Program at Stanford University, followed by Dr. Michael Soulen, Director of the Interventional Oncology Program at the University of Pennsylvania, and Dr. Xavier Keutgen, a Surgeon at the University of Chicago Medical Center and Director of their Neuroendocrine Tumor Program:

Kunz: *"I would say surgery is really the option that we should be thinking about first, and that's because if someone has a localized NET, the best, and curative approach would be surgically removing it."*

Soulen: *"So the first thing I do when I look at a patient is, you know, is this something that's surgically removable. The downside is you have to have surgery, the good side is if you do, it's gone."*

Keutgen: *"If your tumor is localized, so if it has not spread, surgery is the only potential for cure, meaning that the tumor will never come back. We don't have any other therapies that will make the tumor disappear like surgery can."*

And even if it doesn't result in a complete cure, surgery can significantly reduce the amount of tumor in your body.

Keutgen: *"Surgery is the one modality, and the one treatment you can get, if you're a good surgical candidate, that can actually significantly shrink the amount of tumor burden and sort of reset the time clock, versus all these other systemic therapies are mostly exceptionally good at stopping the tumor from growing for a certain amount of time."*

But surgery is not always an option. It really depends on the nature of your particular NET, and also how healthy you are overall.

Here's Dr. Eric Nakakura, a surgeon at the University of California, San Francisco who specializes in operating on NET patients:

Nakakura: *"There's three general things that we consider when we're evaluating someone for surgery. One is the patient themselves – are they fit for major surgery? And that depends on a lot of things like how healthy their heart is, something that we call their 'performance status' – how well they can do basic daily activities such as walking or getting around. And then there are things such as tumor factors, such as we call the anatomy, or sort of like the roadmap of the tumor – can you get the tumor out safely and get it out completely? And then there's the third general factor, what we call the biology of the tumor. Do we think that if we remove the tumor with surgery, it will lead to a durable outcome?"*

Some of this comes down to grade and stage of the tumor. If your cancer is late stage, meaning it has metastasized to parts of the body other than where it began; surgery may no longer be such a good option.

Kunz: *"So if someone is deemed to have metastatic disease, either at diagnosis or later on, surgery is usually not the first best choice – or, I should say the best first choice – occasionally we'll think about using surgery in the setting of metastatic disease, but that requires multidisciplinary input."*

And also, with high-grade NETs – tumors that are growing and spreading quickly, surgery often doesn't make sense.

Keutgen: *"Surgery's not a good option when the tumor is a high-grade tumor, because they usually grow so quickly that actually by the time you do surgery, the patient recovers, you know, the tumor is usually already back. The tumor's back already, what's the point of having done surgery?"*

But a lot of NETs are not high-grade. NETs can be slow-moving, much more so than other kinds of cancer, and this opens up a whole range of other surgical options.

Keutgen: *"It's a slow-growing tumor, so let's say you have a complication and you have to not get any systemic therapy for six months, it's probably not going to make a huge difference down the line.*

If you have a very aggressive cancer and you need to go on chemotherapy, you know – two weeks after surgery – that's a whole different ball game. Because, you know, your tumor's going to grow wildly if you don't go on chemo therapy after surgery, then you think really about doing surgery, because you don't want to get any complication that then delays chemotherapy down the line. But this is not really what we're dealing with NETs. It's a different disease, and I think a lot of the things we do surgically are looked upon with a little bit of perplexity from medical oncologists,

especially those that are not specialized in NETs, because we don't use standardized principals that apply for most cancers when we talk about NETs. NETs are a completely different animal than classic adenocarcinomas, so you have to think outside of the box of the standard oncological principals to treat these patients."

NETs can happen more-or-less anywhere in the body. And because they can often take a long time to be diagnosed, they can be presented for surgery in a wide variety of sizes and places. And so there many different types of surgeries that are used for NETs.

To begin, let's talk about the belly, which contains several of the most common sites for NET primaries – starting with the organs in the gut that are the easiest to operate on, and then moving to the ones that are more complex:

Some of the easiest NETs to remove are those found in the Appendix, because they're treated with a normal appendectomy, one of the most routine surgeries there is.

NAKAKURA: *"So, neuroendocrine tumors of the appendix – fortunately, most people are diagnosed after the fact. That is, the typical patient with an appendiceal neuroendocrine tumor shows up to the hospital with what is thought to be appendicitis. They get their appendix out, and it's not until the pathology results come back that they say, 'lo and behold, you have a small neuroendocrine of the appendix*

that caused your appendicitis, and this is what brought you to the hospital'. If the tumor in the appendix is large, if it's spread to the lymph nodes, or if it's been incompletely resected, sometimes we have to do a more extensive cancer surgery after the simple appendix removal. But for the vast majority of patients with neuroendocrine tumors of the appendix, just removing the appendix itself is sufficient treatment."

Another situation where direct treatment is relatively routine is in the case of many neuroendocrine tumors of the stomach, also known as gastric NETs, which don't require surgery at all, but instead can be removed by a procedure called Endoscopy.

Nakakura: *"Endoscopy is a fiber-optic camera that is introduced through the mouth that can look at the inner lining of the stomach, and through this they can also have devices to remove small tumors. The most common gastric neuroendocrine tumors is something called a type-1 gastric neuroendocrine tumor. Now, these typically arise in patients that have an auto-immune problem, a disorder called atrophic gastritis, or auto-immune gastritis, where their body produces antibodies that attack the acid-producing cells in the stomach. Now, these cells are destroyed by the antibodies, and so the stomach no longer makes the acid. Trying to compensate for this low-acid environment, the stomach releases a hormone called gastrin, to make more acid; but this gastrin hormone also causes growth of the endocrine cells in the lining of the stomach. Now it usually leads to very small, usually many, or multi-*

focal, small tumors in the lining of the stomach. In most patients, these small gastric type-1 neuroendocrine tumors can be removed safely by endoscopy. It's like a 'Pac-man'-type device that basically chomps on the tumor and can pull them out. Grab it, pull it out, and that's it."

Things are a little more complicated when NETs form in the small intestine. Your small intestine is basically a long curvy tube that carries food from your stomach to your large intestine, digesting it all along the way. It's called small because of the diameter of this tube – only about one inch around – but it's massively long, often 16 feet total folded and looped around itself dozens of times.

An interesting thing about small intestine NETs, is that they often have what are called 'multi-focal primaries'. This means that instead of a single primary tumor, there are several small tumors that develop at the same time and all contribute to later metastasis.

Nakakura: *"Fortunately, in most patients, those multi-focal primary tumors are kind of clustered together in a segment of about two feet of intestine. So you can remove that two-foot wedge of intestine and the lymph nodes of that region in one piece.*

And how do you divide the intestine? Well, we have these stapling devices that essentially have two rows of staples,

they staple on either side of a knife, so you staple on both sides of the intestine, and the knife cuts between those two staple lines, and it seals it as it's dividing it.

So you imagine you have a segment of intestine you want to remove, you staple it on one side before the tumor, one side after the tumor, and that essentially gives you like a sausage, or a defined section of intestine. And then you've gotta remove the blood supply. To go across the blood supply, we have these special heating devices that basically seal the vessels and then cut between the area that's been sealed. And so, through the combination of these stapling devices and these heat-sealing devices, we can remove that segment of intestine.

Once that segment is removed, we have to put it back together, right? If you cut off two ends, you have two blind ends. You've got to put them back together. And to put them back together, you can either sew it, just like you're sewing a shirt. You can sew the two ends of the intestine back together and reestablish the 'lumen' or conduit. Or you can also use stapling devices to do the same thing."

Because you have so much small intestine, a two-foot chunk can usually be removed without hurting its ability to function.

The thing about these multi-focal primaries, though, is that there are sometimes a lot of them, and they can be really small

– too small to be seen on a scan. Sometimes the only way to find them, and find the right portion of intestine to remove, is to feel for them with your fingers.

Here's Dr. James Howe, a surgeon and Co-Director of the Neuroendocrine Cancer Clinic at the University of Iowa:

Howe: *"The most important thing is when you get into the abdomen, is to what we call 'run the small bowel', and what that means is to palpate, or feel between your fingers, the entire length of the small bowel. This is usually about 500 centimeters, or 15 feet. If you do a case, say, where you're using metal graspers to feel the intestine, you're often going to miss smaller lesions."*

Nakakura: *"They feel like little BBs, or pellets, that you can feel in the lining of the intestines, but you can't see them on imaging, you can't see them with your eyes, but you can feel them."*

And it may sound like this process – getting to every section of that long, curling, folded tube – would require a really daunting surgery. But thank goodness, that's often not the case.

Keutgen: *"what's called laproscopic or 'keyhole' surgery, that is just a couple of small incisions versus one bigger one. Not everyone is a candidate for laproscopic or minimal-invasive procedure, but we try to do it as often as we can."*

Nakakura: *"And through that small incision, we can still certainly look with a TV camera and evaluate the extent of the disease, we can also palpate and feel the intestine – because the intestine is like a long noodle. You can actually pull the intestine through a small hole and feel it with your fingers, and through that small hole you can remove that wedge of intestine, lymph nodes, and mesenteric mass, and you can sew it back together and put the noodle back into the belly."*

One of the reasons that this minimally invasive surgery might not be possible is if the tumor has grown into a form called a 'mesenteric mass', which is large enough to begin compromising the relationships of the intestine to the blood vessels that keep it healthy. If this mass grows too much, it can become a reason that surgery is no longer possible at all.

Nakakura: *"One thing to think of, is you want to remove the tumor and make sure the intestine is healthy afterwards. And the thing that you need is a blood supply to the intestine and a return from the intestine. Well, this mesenteric mass can kind of creep up along the origin to the blood vessels that supply to the intestines, and if they get to the point where they're actually surrounding the blood vessels – what we call encasement – then it may not be feasible to remove the mass and preserve the blood supply to the intestine. And so, if the tumor gets to the point where we can't remove the tumor, the mesenteric mass, and preserve the blood supply to the main intestine, then surgery is not safe."*

In the best scenario, the tumor is located in the intestine, hasn't spread to the lymph nodes, hasn't caused a mesenteric mass, isn't compromising the blood supply, and you just remove the segment of the intestine that has a tumor in the wall and the lymph nodes in the region to make sure they're not involved, and then you put the intestine back together. And in the ideal situation, you've cured the patient."

Another common location in the gut for NETs to develop is the pancreas, which is an organ that's more-or-less a huge gland located up behind your stomach. It's a factory for producing important chemicals that your body needs to function.

Here's Dr. David Metz, a gastroenterologist and Co-Director of the NET program at the University of Pennsylvania:

Metz: *"The pancreas does two jobs – there's the exocrine pancreas that secretes enzymes for digestion; and there's the endocrine, or hormonal, pancreas that secretes hormones to work with your metabolic control, and the important ones in the pancreas would be insulin, glucagon, somatostatin, etc."*

And while small intestine surgery is relatively simple to perform, surgery on the pancreas is a lot trickier.

Nakakura: *"The pancreas is located more towards your back, or your spine, than from your belly wall. So getting to the pancreas is a challenge."*

The pancreas is also a challenge because it's squishy. It's not made of muscle or some other kind of tough tissue like the stomach or intestine or lungs. It's soft and delicate and not especially conducive to making clean cuts or sewing up with stitches, or the other things we do when we do surgery.

Here's Dr. Myron Schwartz, a surgeon at Mt. Sinai Medical Center in New York City:

Schwartz: *"The pancreas was not meant to hold stitches. It's a very soft organ, and trying to close that duct... you know, pancreas juice, what does it do? It digests things, that's what it's for, and it tends to digest stitches as well."*

The pancreas basically has two parts – a head and a tail. Operating on the tail of the pancreas, also called the distal portion, can be a relatively easy surgery, and can sometimes even be done laparoscopically.

Howe: *"There is a role for laparoscopic removal, which is pretty good for small lesions in the tail of the pancreas. You can also enucleate with a laparoscope, and it's very well*

suited for this distal pancreatectomy. Mobilizing, using graspers, you would divide the pancreas, and then take out the tail of the pancreas with or without the spleen. So, smaller tumors in the tail can be treated this way."

Removing tumors in the head of the pancreas, though, is a much more complicated procedure, requiring a specialized type of surgery called a 'Whipple procedure'. This is because the head of the pancreas is connected to at least three other organs – the stomach, the small intestine, and the gall bladder – and so operating there really requires operating on all of those organs at the same time.

Schwartz: *"The lower part of the bile duct, first part of the intestine, head of the pancreas - they all are an anatomical unit with a single blood vessel that supplies the blood to them. And so that there's no way, certainly in a patient with cancer, when we want to remove everything in what we call an 'en block' way – not cutting close to cancer and risking leaving anything behind – we have to remove those things as a unit."*

Nakakura: *"Now once you remove those structures as a unit, you have to reconnect the stomach to the intestine, you have to reconnect the bile duct to the intestine, and you have to reconnect pancreas to the intestine."*

Schwartz: *"So that it's a real plumbing job hooking up these three things to make sure that everything can function properly."*

Nakakura: *"Decades ago, the surgery was almost abandoned because it was thought to be unsafe, most patients didn't make it through the surgery. But thankfully, through the advances, and one of my mentors, Dr. John Cameron at Johns Hopkins, actually made this a safe procedure. So now-a-days, this is an incredibly routine and safe procedure."*

And for many neuroendocrine tumors that are straightforward, this surgery can be done in three-to-four hours at experienced centers."

Schwartz: *"It's a type of procedure which has become very standard, we do at our place maybe 100 or so a year procedures like this. The risk is now below one percent mortality, though it's a complicated procedure that takes a long time to recover from"*

And risk in recovery, for any kind of pancreas surgery, is the danger that too much of the pancreas will have been removed for the rest of it to continue to function normally. This can cause serious problems because your body is no longer producing all of those enzymes and hormones. An example is immediate, severe diabetes, because you are no longer producing insulin.

An interesting option in many mid-gut NET surgeries is something called 'Enucleation' – which literally means 'removing the center'. It's usually only possible in benign tumors, but sometimes it can be used with malignant NETs because of their slow growth.

Schwartz: *"These tumors are – the well-differentiated ones, we're talking about now, the G1 tumors that are growing very slowly – are very well contained. You can see the border totally clearly, they don't tend to grow into the surrounding tissues like other types of cancers do, and a concept that would be an anathema – would be a surgical sin – to do in any other types of cancer, is what we commonly do in neuroendocrine tumors. It's called 'enucleation', which means, basically, just like a zit, you pop it out. And it's a technique that only applies to neuroendocrine tumors. You don't need to remove a big margin of normal tissue around it like you do in other types of cancers. And this is very useful, especially in the small tumors near the surface of the pancreas.*

You do have to be careful, because the duct system is running through the pancreas, not to get in too deep and make a hole, because then you can have a leak that can persist. But it's a technique that works very well."

Outside of the gut, the most common place for NETs to develop is the lungs. And here too, there are a number of surgical options, depending on the characteristics of the particular tumor.

Here's Dr. Andrew Kaufman, a thoracic surgeon at Mt. Sinai in New York City:

Kaufman: *"We can do a lobectomy, where the anatomic lobe, meaning the airway, artery, and vein to that segment of the lobe is removed. We can do a wedge resection, which means a small piece of lung that's non-anatomic is removed. We can do a pneumonectomy, which we don't like to do because that removes a lot of healthy tissue, but sometimes we have to if it's a central tumor.*

Or, we can do something called a segmentectomy, where it's further out in the lung, but we still take individual airways and blood vessels. There are many different segments in the lung that we can remove individually and save the vast majority of lung tissue. We used to have to do standard thoracotomies, with big incisions and big retractors. We're also able to do these operations now more and more minimally-invasive, to use small incisions, about a centimeter each, and place a video camera in the chest and perform the operation, which obviously has a better cosmetic result at the end and also leads to less post-operative pain."

Many NET patients have metastases, tumors that have spread beyond their original primary site.

Schwartz: *"A large proportion of patients present with metastatic disease at the time of discovery, and so that while we talk about surgery as the curative treatment, that's an option only in a minority of patients with small bowel tumors, they generally have begun to spread at least to the lymph nodes nearby, if not to the liver."*

Keutgen: *"If you have, let's say, a pancreatic or small bowel neuroendocrine tumor that has spread to the liver, you know, a lot of medical oncologists especially those that are not very familiar with this disease will say 'well, you know, you have tumor on your liver, you have Stage 4, there's nothing surgically that can be done for you', and that's actually most often not the case."*

Rattazi: *"I'm Jan Rattazzi, I'm from the Chicago-land area. I'm 66, I was 63 when I was diagnosed. I had a tumor, a NET tumor on my ilium and it had metastasized to my liver. It was back in May of 2016, I had just run a four mile race. I was getting ready for a 10k race. I was about 5.5 miles into my training and I kept having a pain in my lower right abdomen. Just didn't seem right to me. So I did go see the doctor and he told me, oh, I had a virus, that I need to go lay down in bed. So I went back to see him at a later point in time and said, 'Is this still the virus?' And he said,*

'No, we better get a CAT scan done.' So, that led to a diagnosis of a tumor on my liver.

And I'm telling you, the moon and stars aligned for me because the very next day they sent me to the oncologist. That oncologist said, 'I know nothing about NETs, neuroendocrine tumor cancer. I'm going to send you to a specialist in Chicago.' Thank goodness. That team up there did my surgery. It was a nine-hour surgery. They removed part of the ilium, my ascending colon, 11 lymph nodes in the mesentery, three tumors on my liver and my gallbladder.

Within the next couple of days I was up walking around. I walked as much as I could. I'm a runner and I wanted to get back at it. Two-and-a-half weeks post-surgery, I was running. Six weeks post-surgery, I ran a 5k. So for me, I just wanted to get back at it, and I was able to do that because my surgery was a laparoscopic approach also, so I didn't have as much muscular areas cut as a traditional surgery would be.

I'm one of the lucky ones. I only have had one Sandostatin shot and that was prior to surgery. So after surgery I have had nothing, no shots, nothing. I was actually Stage 4, which is a scary thing to hear because with other cancers, you know that's not a good place to be. But with this, through surgery, I am now, 'No Evidence of Disease'."

Let's talk about the liver. The liver is where a large percentage of NETs have the tendency to metastasize first. And, as we've heard, for a lot of NET patients, it's actually the large metastatic tumors in the liver that cause the most serious health problems.

There are multiple liver surgery options with NETs, starting with the enucleation procedures we mentioned earlier.

Nakakura: *"And this is a reason why we can do very extensive surgeries on the liver for patients with neuroendocrine tumors, because we can do this liver-sparing approach, where we just take the tumor out and leave the liver behind."*

But even when it's necessary to remove parts of the liver, the liver is a remarkable organ. It has the ability to continue to function and to heal itself.

Nakakura: *"If your liver is completely healthy – meaning that it doesn't have any disease from hepatitis, cirrhosis, or the effects of chemotherapy – you can remove up to 80% of your liver and patients can do all right. And the reason you can do this is that when you do extensive resections of the liver removal, it has the ability to regenerate where it can over the course of four-to-six weeks, so essentially grow new liver tissue to replace the area that's been removed."*

Now, with other liver cancer, this doesn't work because the tumors would grow back before the liver has a chance to regenerate. So cutting them out would just actually just make things worse. Many NETs, as we keep hearing, are different.

Nakakura: *"So if you can get all the tumors out, and leave the patient with enough functioning liver tissue that the liver can do the things that the liver does, that are essential for life, the median survival could be approaching 10 years in patients where we can remove all or most disease in the liver."*

With NETs we can do something called 'debulking', which means cutting away some, but not all of the tumors in a particular organ.

Keutgen: *"So we actually remove, let's say, 90% of all the tumor in the liver, we leave a very small amount of tumor behind, now you're dealing with a much better situation, because you have a much smaller amount of tumor burden in the liver. So the risk of you getting into liver failure from your tumor in your liver is very little. And over time, with additional systemic therapies, we can keep that liver tumor burden level at a very low percentage."*

Here's Dr. George Fisher, a medical oncologist from Stanford University:

Fisher: *"If you were to imagine that it took 10 years for a tumor the size of a marble to become the size of a*

softball, and say we go ahead and remove three or four softballs worth of tumor down to marble size, it might take five or 10 years before they got back up to that size. That would never be the case with a different type of cancer – with a more aggressive cancer. In fact, more aggressive cancers, like pancreatic adenocarcinoma, if you were to try to remove, you know, five spots in the liver, by the time the person recovered from surgery, they'd probably have 10 or 15 spots in the liver, just because the rest of the cancer is just so aggressive. But neuroendocrine tumors can grow so slowly, that you could debulk a tumor by removing the larger portions of the tumor, knowing that 5% of the disease they have left might take years before it grows large up to cause symptoms again."

Keutgen: *"So, we do what call a 'parenchymal sparing resection', so we try to leave the normal architecture of the liver intact as much as possible. And we literally carve these lesions out one by one, or we burn them with microwave ablation devices in the operating room."*

Here's a question: If you have metastases in your liver, or elsewhere, that are not resectable by surgery, should you still surgically remove the primary tumor? This is a point of debate in the

NET surgical community at the moment, and if you're in that situation, you may hear different opinions from different doctors.

Keutgen: *"The question is whether you should still have the primary tumor that's in your small bowel removed if you can't surgically remove that disease in your liver. That's a controversial subject. The data that we have right now suggests that even if the liver cannot be addressed surgically by removing the primary tumor, you may actually improve survival long-term. One of the theories of why that is, is because we think that because the tumor cells spread from the primary tumor and go to the liver. By removing the source of spreading - the liver metastases, or the tumor in the liver - it will be less likely to grow more rapidly, because there will be less fresh tumor cells that get fed constantly into the liver from the primary tumor. But that is a controversial subject, no question. I'm in favor of doing it, and I'm pretty aggressive when it comes to these things."*

Schwartz: *"But this has really become a question now, I think it's not as totally clear. There are cases where the tumor in the small bowel can cause obstructions and so forth, of course, you remove the tumors in those cases. But there is certainly not a proven survival benefit to doing this. And in fact, at this point there's actually a trial underway, based in Europe, trying to figure this out."*

Soulen: *"More controversial if you have a P-NET, because A. operating on the pancreas is much more hazardous than on the bowel, and B. it's highly unlikely that that tumor, by virtue of its location, is ever going to cause a problem. So, as a general rule here, if it's an easy pancreas operation, like the tail, we'll resect. But if it's complicated, like it's in the head and you would need a Whipple, we often will not. It depends upon the case."*

With any surgery, there will be a recovery period afterwards. And of course, how long this is and what's involved will vary depending on the kind of surgery you've had.

Nakakura: *"For the typical patient that undergoes a surgery for a small intestine or illium neuroendocrine tumor, the typical time in the hospital is on average three to five days. Now, what keeps people in the hospital is their ability to eat and control their pain. If we're able to do this through the minimally-invasive, or through the small incisions, oftentimes they can get out within three days. If you make the bigger incision, usually it's the pain that keeps them in the hospital for up to about five days."*

For patients that undergo surgery of the pancreas, if it's a left-sided removal, which is the distal pancreatectomy, often patients can undergo a minimally-invasive or laparoscopic approach for that, and those patients are in the hospital for three to five days. For patients that undergo the Whipple procedure, the more extensive

procedure, the average time in the hospital is about one week. And the things that keep them in the hospital is pain control, ability to eat, and also just monitoring for any kind of leakages of fluid from the connections we make."

Recovery time for liver surgery is similar to pancreas surgery.

Keutgen: *"The recovery time in the hospital depends a little bit on whether your GI tract starts working rapidly or whether it takes a little longer, but I usually tell my patients after liver resections that they have to think about being in the hospital for anywhere from four to seven days."*

And there's additional recovery time at home before you can be back to full strength.

Nakakura: *"After any major surgery, although patients may go home (in) under a week, it usually takes a good three months before they feel like they're back to their normal self."*

Aside from surgery, there's another option for treating NET metastases directly, particularly in the liver. This is a family of treatments called 'Interventional Radiology' or 'IR' for short, and they're often used when liver surgery is not considered a good option.

Dr. Soulen performs these kinds of procedures on NET patients at the University of Pennsylvania:

Soulen: *"Interventional Radiology is a specialty where we do minimally-invasive, image-guided procedures – so-called 'band-aid surgery'. So, basically, instead of like a surgeon using a scalpel, we insert little devices like catheters and wires and needles into patients using some kind of imaging guidance, could be ultrasound or X-ray or MRI or CAT Scan, and we do that to get to tumors inside the body and treat them in a way that doesn't involve making an incision. So these therapies are minimally-invasive, they're largely painless, you end up with a band-aid, and oftentimes you go home the same day you have the procedure, or maybe you have an overnight stay."*

There are two basic categories of IR treatment used for cancer – ablation and embolization. The first of these, ablation, is simpler – you find a tumor and basically burn it out using a very small instrument with a tip that can be made very hot. While this is sometimes used with NETs, the second type, embolization, is used more frequently.

Embolizations are procedures designed to cut off blood flow. And they work particularly well for liver NETs, because of a peculiar characteristic of these tumors.

All tumors, like all organs, need blood to survive, so they hook themselves up to one of the blood vessels that feeds the organ they're attached to. There are two major blood vessels that

attach to the liver, the portal vein and the hepatic artery. And while healthy liver cells draw most of their blood from the vein, liver tumors draw just about all of their blood from the artery.

Soulen: *"So we take advantage of that by catheterizing the artery to the liver, finding the branches that feed the tumor, and then you can do many things."*

Here's Dr. Riad Salem, an interventional radiologist at Northwestern University in Chicago:

Salem: *"And these things come in three major forms, the first one we call bland embolization, which is you inject these inert particles and they starve the tumor, they decrease the blood supply, and they shrink the tumor. The other one is called 'chemoembolization', where you add a chemotherapeutic drug. You do the exact same thing, you get into the tumor, you inject a chemotherapeutic drug with those particles, and you have a combination effect. And the third one is radioembolization, that is radiation therapy injected directly into the tumor."*

And neuroendocrine tumors are ideally suited for embelotherapy, because they are very rich in blood supply. So whatever you inject will concentrate significantly, and there will be little effect outside that area of injection."

Often in NET treatment, the choice comes down to one of those latter two options – either chemoembolization or radioembolization.

Soulen: *“So when I talk to patients about that, I say you have two choices – ‘quick and sick’ or ‘slow and glow’. So when you do embolization or chemoembolization, it’s quick, right? I mean the procedure is the treatment, I catheterize you, I find out what’s feeding the tumor, I plug ‘em up, the tumor dies that day. And then when you’re done, you just wait another month and get a scan and you know whether it worked or not. But nine out of 10 people get what’s called ‘post-embolization syndrome’, which is this combination of pain, nausea, maybe vomiting, fever, fatigue, loss of appetite, and basically feel crappy for two to four weeks.*

Radioembolization – what people like about radioembolization – is you don’t get sick. Half the people have no side effects at all, 95% get treated as an outpatient and go home the same day. So, very well-tolerated therapy, but it takes three months to see if it worked or not, because radiation works very slowly. So, some people, quality of life is super important, they don’t want to be sick – maybe they’re frail, maybe they’re a caretaker for someone else in the family and they need to be fit, maybe they work full time and they can’t afford to be out of work – and they’ll choose ‘slow and glow’ for quality of life issues. Other people are like, ‘No, I want my tumor dead tomorrow, and I’m willing to tolerate the

side effects to know my cancer is dead tomorrow', and they go for 'quick and sick'."

For a long time, these were presented as equivalent options but some recent studies have shown potential long-term side effects from radioembolization – the 'slow and glow' option – where the radioactive material in the liver can cause problems many years after the treatment was completed. This research is ongoing though, and many doctors still use each of these therapies, depending on the particular case.

Soulen: *"I now tell patients that I have significant reservations about radioembolizations as a first-line therapy, and I basically would not recommend that except in specific circumstances. But in general, I say you should go with bland or chemoembolization first.*

If that doesn't work, I say, 'OK, then we'll consider radioembolization as a second-line therapy', but now we're layering on a layer of risk."

There are a lot of different options, and some subtle and important choices to be made about how to proceed. That's why it's important to be working with a medical team that specializes in working with NETs, knowing how find right treatment for your tumor, and performing that treatment properly.

Salem: *"The technique is very important, meticulous knowledge of the disease condition is important, and experience is very, very important."*

Nakakura: *"Experience matters. How many patients you see with the disease, how you're able to diagnose a patient, how you're able to assess the resectability status, how are you going to be able to recommend the correct surgery, and more importantly, how do you select patients who shouldn't get an operation. So I think the decision to not operate is just as important as the decision to operate, and this is where I think experience is critical."*

Farrell: *"My name is Anne Farrell. I'm from Denver. In August of 2010 I started having lots of pains in my stomach. I wasn't able to eat much, I was losing weight and really didn't want to eat or drink. And I went to my internal medicine doctor who referred me to a gastro doctor and they did all the usual tests, the colonoscopy, endoscopy, and couldn't see what was the matter. So I had a CT scan, and the gastro doctor didn't see any problem, nor did the radiologist. But the chief resident radiologist said he thought he saw something and that I should take my records to a surgeon. So that's what I did. And the surgeon had the opinion that maybe I had NET cancer of the small intestine. They cut me open and went in and began to take out what they could. What was causing discomfort was a blockage due to a tumor in my small bowel, but the main tumor, the largest tumor was wrapped around a very major*

blood vessel. So at that time in 2010, the surgeon decided that it was too dangerous to cut that out. The surgeon did not give me a bright prognosis. He told my family that he thought I had about 18 months to live, but I also had a second surgery thanks to NET Research Foundation. I went to one of their conferences and heard a Stanford surgeon talking about a case that he had done, and I thought it sounded exactly like mine, i.e. the tumor was wrapped around the major blood vessel. And he described doing surgery with another surgeon and how they were able to remove this tumor without any bad consequences. And so, then I went to see him and had that surgery four years after my first surgery. They were able to take out the major tumor as well as I had three lesions in my liver that they also too - they cut out and one they zapped, I call it.

So two things, I think, you know, my mind was put more at ease that I'm not going to leave here tomorrow. And then also my physical symptoms became better. I think I'm doing very well. As a matter of fact, I used to see the oncologist every month, but my CT scans and my appointment with him are now every six months. So that leads me to believe that he thinks that I'm doing well."

Next time, we'll move beyond surgery and IR, and into the fascinating world of nuclear medicine.

Thank you, listener, for tuning into NET Wise. My name is Laran Hyder. I'm the Director of Education and Outreach for the Neuroendocrine Tumor Research Foundation. I executive produced and co-wrote this series. It was produced and co-written by David Hoffman of CitizenRacecar. This episode was made possible by the generous support of Advanced Accelerator Applications, a Novartis Company, Lexicon Pharmaceuticals, and the Vincent E. Taylor Patient Education Fund. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. 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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