Episode 21 – "What to Know About Small Bowel NETs" with Dr. David Zhen
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Lisa Yen:

Welcome to the LACNETS podcast. I'm your host, Lisa Yen. I'm the LACNETS, Director of Programs and Outreach, as well as a caregiver and advocate for my husband who is living with NET. In each podcast episode, we talk to a NET expert who answers your top 10 questions. This podcast is for educational purposes only and does not constitute medical advice. Please discuss your questions and concerns with your physician.

Lisa Yen:

Welcome, everyone to today's episode of the LACNETS Podcast. I'm really excited to introduce our speaker for today, Dr. David Zhen. Dr. David Zhen is a medical oncologist from Fred Hutch Cancer Center in Seattle, Washington who specializes in treating patients with gastrointestinal cancers. In addition to seeing NET patients, his research centers around the development of clinical trials evaluating new therapies and combination approaches for the treatment of patients with gastrointestinal cancers, particularly pancreatic and gastroesophageal cancers. He's also conducting research to understand the interactions of the immune system in gastrointestinal cancers and how this can be manipulated to improve upon the response to immunotherapy drugs called checkpoint inhibitors, which block a braking system that cancers use to tamp down the immune response. And I know Dr. Zhen is going to tell us a little bit more about this. This comes into play with one of the clinical trials that he's launching.

And I had the privilege and the honor of meeting Dr. Zhen in 2022 at a NANETS symposium in Portland. And I was really impressed by Dr. Zhen's passion for NET and for the patient community as well as clinical research. I really appreciated how well he explains things to the community. And I'm just really excited about the program you're building up at Fred Hutch Cancer Center in Seattle and for the greater Northwest region, and how that adds a lot to that region for the patient community, and for our NET patient community as a whole. One fun fact I want to add about Dr. Zhen is that he loves being near water. So, it really serves him well that he moved from Michigan to Washington so that he can sail regularly with some friends.

So, Dr. Zhen, welcome to our broadcast. And I invite you to share anything about yourself. And also tell us a little bit about how you got involved in the NET world.

Dr. David Zhen:
Thank you, Lisa, and also to LACNETS for having me today. I would say my journey started with neuroendocrine tumors during my oncology training when I was at the University of Michigan. And obviously, I knew right away that I was very interested in GI cancers, particularly because my grandfather had pancreatic cancer, so I have a personal connection there. But ultimately, I became interested during my training in neuroendocrine tumors when I started caring for such patients, and I think what I found very interesting was that I learned very quickly that this is what we call and we'll say it many times, a heterogeneous disease, meaning that even when we do have some knowledge about what the cancer is, it's very different in each person. It's a very complicated process in caring for patients. But then also, I can personalize the process for each of the patients, which I think gives me a lot of incentive to care for such patients. And I just find these patients very thankful in terms for all their care. And so, I've always had a little bit of an interest. And I think that kind of developed further when I became a full faculty member at the Fred Hutchinson Cancer Center and University of Washington, where I started doing more research. And as Lisa mentioned, there's a national trial that I'm running through one of the National Cancer Institute or NCI cooperative groups called SWOG. And with that, I started to build relationships within the neuroendocrine community, as well as with patients. And I think with that, that just spurred to the development of a neuroendocrine tumor board and a neuroendocrine program at Fred Hutch. And that's kind of where we are right now.

Lisa Yen:
Yeah, well, thank you for that work in this area. One thing I really appreciated from your presentation was that slide where you talked about the multidisciplinary tumor board, and you had the patient at the center, and how important that is for all of us. And we really appreciate that.

Dr. David Zhen:
Yeah, absolutely.

Lisa Yen:

Well, thank you for that focus. And with that, how about we dive into the 10 questions for today?

Dr. David Zhen:

Yeah, sounds great.

Lisa Yen:
Okay, so as you know, our topic is small bowel net. And I was talking to you a little bit earlier. A lot of times in our conferences and educational programs in general, to be efficient in time, to be able to be inclusive for everyone, we kind of lump all the NETS together. So, this is our opportunity to separate them because we know as you were talking about the heterogeneity and how there are differences. So gastric NETS, small bowel NETS, pancreatic NETS, lung NETS, all the different NETS, are different. So, today's topic is really to focus on just small bowel NET. So, the first question for today is, what are small bowel nets and where are they located?

Dr. David Zhen:

So small bowel NETS are neuroendocrine tumors or NETS that start or originate in the small intestine, which basically that's very many feet of bowel that exists. So, this is in the middle between your large intestine, what we call the colon and then also below the upper parts of the GI tract, which includes the stomach and the esophagus. So really, we're talking about a lot of different parts of the small intestine and within the small intestine, we can divide it into different parts. And if we want to get more granular in neuroendocrine tumors, we have what we call duodenal small bowel neuroendocrine tumors, which are kind of the more front portion of the small intestine. Then we have jejunum, which has the many feet in the middle, and then we have the ileum, which is actually where the vast majority of patients often develop their tumors, is in the last third portion of the small intestinal. And so, because of their location, that's what we call small intestinal nets. But there's a lot of different parts to it as well.

Lisa Yen:
Yeah, thanks for defining those terms, because that might be the first time a patient has heard the term ***ileum*** or ***duodenum***, when they're first diagnosed. And you kind of talked about those three? Could you explain a little bit more about how small bowel NETS are found?

Dr. David Zhen:
So, I think each person is different in terms of how they're found. So, I think more of the classical symptoms that we would expect, if you have a mass, let's say in the small intestine, you would imagine that patients may have pain, discomfort. We also worry about when the masses are in the intestines that they can cause bowel blockages, what we have a medical term of what we call a ***bowel obstruction***. So sometimes patients, the tumors have gotten to a size or in a nature that they blocked the bowels. And that may manifest as people not having bowel movements anymore or changes in their bowel habits. They may have decreased appetite. They may have nausea, vomiting, and that kind of thing. And we might expect maybe weight loss, just like what we might expect with any cancer. So those would be typical symptoms we might see, although I will tell you in my own clinical practice, as well as many people who care for NETS is that many of the patients that walk in the door might not have any symptoms. They might actually have very vague symptoms, and the vagueness of the symptoms could be either no symptoms whatsoever so patients might end up getting a scan for another reason and we find a tumor that's in their body.

We know that neuroendocrine tumors, these are cancers that come from neuroendocrine cells. And the job of neuroendocrine cells in your body is to make hormones which basically are the chemical messengers of the body. So basically, how I explain to patients is that these are chemicals then that allows your organs to communicate with each other 24 hours a day. And why that's all relevant is because in some patients, not all, they may have what we call ***carcinoid syndrome***, where what happens with that is the tumors are producing too much of a specific hormone. In carcinoid syndrome, usually it's ***serotonin***. And that may lead to symptoms such as diarrhea, facial flushing, it might affect the airways, where people have asthma like attacks and such like that. And so, some patients might present like that. And that can be a challenge because some of our neuroendocrine patients may go on with the symptoms for many years. And the symptoms can mimic other conditions like what we might say inflammatory bowel disease, or irritable bowel disease, or they might think they're just having asthma. And they get workup and they don't really know what's causing the symptoms, until eventually they might see a NET specialist who figures out hey, you know, there may be a possibility. So, at the end of the day, there's a wide range of symptoms that could occur, but those would probably be the ones that we think about the most.

Lisa Yen:
I'm sure there are listeners that are tuning in, and this might really resonate with them, that they were diagnosed with an obstruction or incidentally from another scan. It's kind of scary for patients to be like, "I was so healthy for all my life. What else could I have done differently?"

Dr. David Zhen:
You know, that's a big counseling point, when I meet patients for the first time, just like anybody with cancer, it's like, "What did I do wrong?" Like, "Did I cause all of this?" And for the vast majority of cases is really nothing anything that the patient did, and the vast majority of my patients are healthy individuals who have done everything right in life. But just like with any cancer, oftentimes, it's bad luck. It just ends up happening.

Lisa Yen:
Yeah, bad luck. So that really leads to the next question, "What types of lab, scans, or testing are done to determine if someone has small bowel NET?" And I guess one of the big questions that comes up often, you know, you're talking about healthy patients, people who might go to their doctor and get their regular endoscopy and colonoscopy. Why is it not found on endoscopy and colonoscopy?

Dr. David Zhen:
Yeah, that's a great question. So unlike neuroendocrine tumors that start in the colon, where we can detect those with basically a scope called a colonoscopy, which is looking at the large intestine. And likewise, if you had a stomach neuroendocrine tumor, and then maybe for some select patients, the first part of the small intestine that I refer to as to as the ***duodenum***. In some cases, you can detect those as well with an upper endoscopy or what we call an ***EGD***. But the problem is that the vast majority of neuroendocrine tumors in the small intestine, as I mentioned, happen either in the middle region, or they're near the end. And unfortunately, those are areas where the current scopes, the upper endoscopy and the lower endoscopy, or the colonoscopy don't end up reaching those areas. And because they don't end up reaching those areas, oftentimes, you're not going to find those tumors. And so, really how we often detect a lot of these tumors is with standard imaging. And the standard imaging usually involves in most patients at the beginning, what we call a CT or a CAT scan, where basically we're taking x-rays or slices of the body. And when then we end up doing those images and we find a tumor in the small intestines.

Lisa Yen:
So, you mentioned CT or CAT scan, is there a particular type of CT or CAT scan or particular kind of contrast people should be getting when they get this?

Dr. David Zhen:
Great question, I think for the most part just to take a step back. When we think about CT or CAT scans, normally these are given with IV contrast. So, we give a specific dye that allows us to visualize the organs as well as the tumor a little bit better. And in most cases, when we do a traditional CAT scan, most of them is what we call a ***single-phase***. So, in other words, when you're getting your scan, the radiologist or radiology technician will administer IV contrast. And typically, they have a protocol where they know when to time to take the pictures. And when they take the pictures, they usually time it in a fashion such that we expect the contrast to be going through the veins or otherwise leaving the organs or leaving the tumors. And this is most relevant for tumors when we're trying to visualize in the liver.

And while that really is helpful for the vast majority of the cases for detecting a lot of different things, in neuroendocrine tumors, actually, where we see tumors the best, particularly if they end up do spreading to the liver, is when we take the pictures as the contrast is going through the arteries or feeding into the organ, or feeding into the tumor. And so really, for patients with neuroendocrine tumors, we often emphasize when we do CAT scans, we actually specify that we want what we call a ***multi-phase CAT scan***, meaning that in addition to the standard, just taking the pictures as they're going through the venous system, we also take an extra set of pictures as we expect them to [be] going through the arteries. And because when we do that, we actually increase our detection rate and often find tumors much better. And that allows us to also in the future, depending on what treatment we might end up doing, be able to compare things that are there as well.

Lisa Yen:
I explained that so clearly, and in a way that's really easy to understand. I really appreciate that a lot. So, another question that comes up whether someone is found to have something on their multi-phase CAT scan, or on another CAT scan, or just they think that they might have it or their doctors suspect it, what other labs and testing would you recommend?

Dr. David Zhen:
So, I think the other testing that includes, there are specialized imaging that we end up doing as well, too. So, as I talked about, when we think about neuroendocrine tumors, we have the tumor itself that physically could cause problems. But then the tumors themselves are functional cells. In other words, they make hormones. And so, along those lines in terms of detecting the potential possibility that the tumors may be making specific hormones, we have what we call ***functional imaging***. And what functional imaging refers to is trying to assess whether the tumors are making specific hormones. And that information is important for us to primarily one help with detection, but then also help with decision on potential treatment options for that specific patient.

And what I'm referring to, as many people may know, is what we call a ***DOTATATE PET scan***. So, this is different from a traditional PET scan. So, you may hear about other PET scans. And what other PET scans are is usually what we call an ***FDG PET scan***. And what that is, is essentially taking the same technology of a CAT scan. But instead we're now using a different type of contrast material. And we're using a radioactive molecule and this radioactive molecule in FDG PET scans is basically radioactive sugar. So, the idea is that all cells in our body need sugar for fuel. But cancer cells might take up a little bit more sugar just because they need that to support their growth. And so FDG PET scans are basically saying when tumors take up this radioactive blood sugar, we can detect tumors there. Well, what a DOTATATE PET scan is a dedicated scan only for neuroendocrine patients, because we've refined the FDG PET technology to change the radioactive molecule into a molecule that recognizes a specific hormone, in this case, what we call ***somatostatin receptors***. And so, we're looking for this specific hormone on the surface of neuroendocrine cells. And that helps us detect one where the tumors may be in the body. And then, likewise also helped us determine treatment options, which we will talk a little bit later. So that's regards to scans.

And then other things that we might check from a bloodwork standpoint is that we can check some of the hormones from the blood. And I think in small intestinal neuroendocrine tumors, there's things like what we may refer to as ***5HIAA***, which oftentimes, we may check in the urine. Those are breakdown products of serotonin. There's serotonin that we can check directly in the blood. So various, a lot of different types of hormones that we can check in that information. Sometimes, one, helps us figure out whether patients' symptoms may be related to hormone excess or not, because sometimes the

symptoms may be related to other things. And then sometimes we might use some of these hormones also for monitoring of their disease.

Lisa Yen:
Yeah, so you mentioned 5HIAA. Does it matter whether they get it from their blood or urine?

Dr David Zhen:
So, I think traditionally, we've oftentimes done it in the blood. When I was in training, that's how we've done it a lot. But what I will say is that it's often cumbersome, because things can often affect these tests. And a lot of times we end up doing a 24-hour urine, so forces patients to basically collect their urine at home for 24 hours a day, which often can be cumbersome. There are newer, refined more tests now that we can make it simpler to do it on the blood as well, too. I will say though, some not all centers have jumped, for example, at the Fred Hutch, I think, because of our laboratory, we're still not quite there yet with the blood. I know some centers are there as well, but we are working on trying to hopefully get that test as well.

Lisa Yen:
Convenience matters to patients. So, you mentioned the 5HIAA. What about other tumor markers –I know that might be controversial—chromogranin, other types of lab work?

Dr. David Zhen:
Yeah. Chromogranin A is one of the other hormones that we can check, and it's been around for quite a while. And we often, I would say, every provider often checks it including myself, but I think even leaders within the neuroendocrine field are questioning sometimes the value as well too, because just like with all the other hormones that we check for neuroendocrine tumors, these can fluctuate for many different reasons. And the thing about the chromogranin A, again, it's what we call a ***tumor marker***. So just like other cancers, we have other blood tests that we can check where the idea here is that these are proteins or substances that the tumor may make. So, if there's more tumor, we expect the number to go up, if there's less tumor that we expect the number to go down. So, we would expect the same thing to happen with chromogranin A. The difficult part in neuroendocrine tumors is that sometimes even when the scans are not showing any change, we can see the chromogranin A go up and down. And obviously, those increases or decreases can cause anxiety for both patients and also providers alike. And it's very challenging because we oftentimes have to explain that the numbers sometimes don't always mean that your disease is getting better or worse and might not even have any relevance. But what I do find helpful is that we do, still do check the markers just because we might look at long term trends. So, you know, little blips up and down might not really matter. But if we see a continuous trend up or down, sometimes that might be more relevant.

Lisa Yen:
Okay, so if someone's coming to see you with a presumed diagnosis of small bowel and that it sounds like you'd like a multi-phase CT scan, a DOTATATE PET scan, a 5HIAA, and a chromogranin A. Anything else you'd like to add to that?

Dr. David Zhen:
No, I think those are pretty much our standard tests every now and then. If, for example, we're worried about other sites, we might end up doing an endoscopy and I'm not referring to an upper endoscopy or lower endoscopy. Sometimes there's other scopes, for example, what we call a ***capsule endoscopy***, where you swallow a pill, and that sometimes takes pictures of the small intestine. There's more

advanced endoscopy is what we call ***double balloon enteroscopy***, which specialized centers sometimes can do, where basically what they do is they try to extend the scope deeper into the small intestine, they're not gonna be able to visualize the whole thing. But sometimes if we're really questioning the diagnosis, and we haven't found the tumor, sometimes we might do those things. But at the end of the day, oftentimes, we'll see the masses on the scan. So instead of subjecting patients to such invasive procedures, we often can just make a diagnosis based on scans.

Lisa Yen:
And I know sometimes someone comes with liver tumors, and they don't know where the primary side is. So, I'm wondering if those are the same scans and labs you would use to try to see if it's small bowel.

Dr. David Zhen:
So oftentimes, how we make the distinction of where we think the source is, for example, if we see liver metastasis, is often based on the imaging. So usually oncology, we think about what we say the clinical picture is, even though there's always many different possibilities—two, or three or 10 things could be going on. Usually, that's not the most common, so we try to make the simplest explanation. So oftentimes, if we see masses in the liver, more than 90% of the time, that's usually spread of cancer from somewhere else. So, if we take an image, and we've just biopsied the liver, but let's say we take an image, and then we find a big tumor in the small intestine, that's usually pretty consistent that we would say that's the source. Sometimes there may be situations where maybe the mass in the small intestine is not as big and now, we're kind of questioning is that really a source? Maybe we need to do a little bit more homework to figure out if it's coming from a different organ. But that's usually how we make that determination.

Lisa Yen:
Thanks for all of this. I know there's a lot in that whole area of workup, the labs and scanning and testing. So how about this next question: “What are some ways that small bowel NETs differ from other types of NET?”

Dr. David Zhen:
So, I think compared to other neuroendocrine tumors, and we think about GI neuroendocrine tumors, we often lump buckets into pancreatic neuroendocrine tumors and everything else. And the reason we historically think about it that way is that that affects a little bit our treatment options. And with regards to that for pancreatic neuroendocrine tumors, we know oftentimes other agents, for example, like chemotherapy pills or even other different type of targeted agents respond a little better or have a little bit more effectiveness in pancreatic neuroendocrine tumors. However, small bowel neuroendocrine tumors, sometimes those treatments aren't as effective. And that's important to know, because obviously, we don't want to give patients treatments that may not be as effective and also expose them to those side effects. But likewise, I think even though we might think, okay, well, maybe there's different treatment options or maybe less treatment options. The other component is that most of the time for the vast majority of small bowel neuroendocrine tumors, these are usually often more slow growing tumors as compared to let's say, pancreatic neuroendocrine tumor. So, there's a little bit of a plus side from that. And there are patients that oftentimes that, even though everybody's courses a little bit different, these are patients who are living with these diseases for many years. So oftentimes, we're able to convert this into more of a chronic disease.

Lisa Yen:

Yeah. That's hopeful. So, speaking of converting it into chronic disease and the treatments, how do you decide if Ythe small bowel NETs can be surgically removed? And what type of surgeon would make that determination?

Dr. David Zhen:
It's a complex question. And that's why oftentimes when we think about the management of neuroendocrine tumors, and what spurred my interest for developing a neuroendocrine program is as I mentioned, one person can't do it all. You need multiples sets of eyes here. And what I mean by that is that's why tumor boards are very important because we can have, not only my medical oncology colleagues look at things, but then I also need other specialists: surgeons, I might need radiation oncologists. I need radiologists who can review the scans and tell me where things are. And so, from that perspective in terms of decisions, in terms of whether a surgery is possible or not, that's where this multidisciplinary discussion is important, right? So, one is I need the surgeon's perspective. Anatomically, do they think they can actually reach the tumor and actually cut it all out and reconnect things appropriately, that the patient is going to continue to do well? And then also, I kind of need to know how much are they going to resect? Because the more that they're going to resect, it's probably going to affect the patient's quality of life. And we've got to think about when patients are living with a chronic disease, yes, we can probably take care of the tumor. But if the surgery is going to lead to more debilitating consequences down the road, then we might have to question, "Is this something that we need to really do?" The risks might outweigh the benefits at that point, right? So, all those kinds of questions and discussions come into play. So, one is the technical challenges. Two is the quality of life perspective as well.

And then, in terms of the surgeons that have to be involved. Oftentimes, these require cancer oncologic surgeons. So surgeons who are trained in doing cancer related surgeries, knowing not only how to remove the tumor, but also removing adequate number of lymph nodes to make sure that we've gotten rid of all the tumor, where they need to really go to make sure they've done a complete resection. And, you know, in terms of training for surgeons, oftentimes at academic centers, they're very specialized to different parts. So, for the small intestine, sometimes we might have overlap with general surgeons, but if, for example, duodenum, the first part of the small intestine, they're relatively close to some of the structures near the liver. So sometimes we actually have to get our liver surgeons involved. And then depending on where tumors may be, for example, in women, where sometimes these tumors are pretty close to other structures, for example, the ovaries and uterus, sometimes we may have to get involved gynecological surgeons as well. So, it really depends on the location of the tumor, spread of the tumors, and involving other structures. And that's how we make decisions about what types of specialties or special types of surgeons, we might need to get involved.

Lisa Yen:
You brought up the comment about adequate lymph nodes, I was wondering, what are the number of lymph nodes that should be resected?

Dr. David Zhen:
Yeah, I think we often extrapolate from a lot of different cancers. For example, in colon cancer, we have usually an average about 12 or more, if not greater, to try to remove those. And I would say, oftentimes, we might do that for small bowel neuroendocrine tumors, what you'll see here is obviously, usually the more lymph nodes that we remove, usually the better in terms of ensuring that we get rid of disease. However, at the same time, too, depending on where the location is, and how much you have to

remove, it also means a more morbid, in other words, a more aggressive type of surgery, right? And that might have some quality of life implications as well.

Lisa Yen:
Yeah, thank you for clarifying. And you also mentioned bowel obstruction. So, there are many people who are diagnosed when they first get a bowel obstruction. Is that a time when a surgeon could just resect everything?

Dr. David Zhen:
Oftentimes, if they can, they try to, but sometimes, depending on the situation, or how the patient is doing, if, let's say the bowel obstruction, because what we worry about with the bowel obstruction is that it can really sometimes choke on the bowel and cause the bowel to die off. And so sometimes if patients are extremely sick because of that, which, not a common situation, but just an example of a situation where emergently, we might have to really just focus on getting rid of the dead bowel and that kind of thing. That's where we might focus on just that resection, and then let the patients calm down and get healthier and then maybe down the road, we might do a more extensive resection. But oftentimes, if a diagnosis of neuroendocrine tumors have been made, there's a specialized surgeon who's already involved. And they know that potentially we'll have to resect the primary but if they already know that there's other cancers, and we've staged the patient appropriately, yeah, we like to try to do one operation and consolidate things as much as possible.

Lisa Yen:
Okay. One other thing I didn't hear you mentioned about what if they have tumors in the peritoneum or mesentery? How do you as a medical oncologist weigh that in?

Dr. David Zhen:
Well, that's where discussion between the medical oncologist and surgeon happens. And especially when you get spread to the peritoneum, I think sometimes you need a little bit more specialized surgeons who are comfortable with doing that, because I would say that gets a little bit more of a technical surgery where we have to cut tumors out of the peritoneum. And that's a more aggressive surgery that's often done by very specialized surgeons who knows about the risks and benefits of doing those kinds of things. And for example, at the Fred Hutch, we have surgeons who do those kind of things for neuroendocrine tumor patients, but we also have surgeons who are dedicated and trained to do what we call ***cytoreductive surgery*** within the peritoneum and they know how to do those types of surgeries. So, depending on the volume of disease. I think it depends on a couple of things that we take into account number one is volume of disease, so obviously, the less amount of disease that's in the belly, you could imagine that you could do a surgery versus if you have a significant amount of tumor, where if there's that much tumor, sometimes you're not going to be able to resect all of it so you're probably going to have to leave some disease behind. And then too, is also the disease biology. So, in other words, if we're going to do aggressive surgery, we also want to make sure this is more of a slow-growing type of tumor, because then that makes sense versus if we have a more fast-growing tumor, then if you do a big surgery, that cancer is probably going to come right back quickly. And so, we might have to emphasize more what we call systemic treatments or medical treatments to get that under control.

Lisa Yen:
Thanks for extending all that it sounds kind of complicated. Like there's all these different types of surgeons that you might have seeing the NET patients. So how would a patient know where to go?

Dr. David Zhen:
Oftentimes, I think what's important for NET patients is, LACNETS and NANETS have always advocated for, is making sure that you at least get a consultation at a NET expert center. So just having that case reviewed, even once just by that group. And just so that way you get a lot of different opinions and the tumor board or multidisciplinary discussion, just so you know that you're headed in the right direction. And oftentimes, if you're heading in the right direction, then we can just say that, and you can continue your care with providers who you may trust and work closer to home.

Lisa Yen:
Yeah, thanks for that. Definitely getting review by an expert center, it could completely change things. So, we talked a lot about surgery. How are small bowel NETs treated medically?

Dr. David Zhen:
So, we have various different types of medical treatments for small bowel neuroendocrine tumors. I think one of our mainstay medical treatments that we have, as I mentioned, small bowel neuroendocrine tumors often make a certain hormone on the surface of cells, somatostatin receptors. So, we have drugs that can target those things. So when they bind to these receptors on the neuroendocrine tumor cells, what it does is, if patients have symptoms, what we call ***carcinoid syndrome***, they're making too much hormone, one of the purpose of the drugs is to try to suppress that hormone production and allow quality of life better for patients. And then too, is also we know these drugs, they can help to control tumors. In other words, slow down to growth. So, if something's already slow growing, we try to make it even more slow growing, and the drugs that we have are where we call ***somatostatin analogues***. So, these are the drugs that bind to the somatostatin receptors. And we have two really major drugs that we have. One is called ***octreotide***, which has been around for a long time. We also have another drug called ***lanreotide***. These are both injections that typically are given in the muscle area of the buttock. They're given once a month. And essentially, they serve the two purposes, as we discussed. And oftentimes, these are treatments that most patients can tolerate pretty well. And oftentimes, it's one of our mainstay treatments that we start off on.

Then as we go down the road. If, let's say, we start with somatostatin analogs, if the cancers are growing, or maybe hormone symptoms are not being controlled, there's other treatments that we can use. And the other treatments that we have come in different flavors. I think one of the main treatments that many people are excited about is what we call ***peptide receptor radionuclide therapy***, or what we call ***PRRT***. The drugs that we have the brand name is ***Lutathera***. The idea here is really the same technology that we talked about the DOTATATE PET scan, where we use a radioactive dye to detect tumors. Well, what if we now change the technology? Instead of using it for detection, what if we use that same technology to actually go kill tumors? And so, what we're doing is we're giving an IV drug, and these are drugs that recognize the somatostatin receptors. But now these are radiation particles. So, we're delivering radiation and selectively delivering them to tumors that are making the somatostatin receptors.

And there's a large study called the ***NETTER-1 trial*** that was published several years back. And this was a treatment when I was in training that was available only in Europe, and I actually sent patients to Europe to get the treatment. It's nice now that we have it in the United States. And so, we can use that as a treatment. And then, we also have oral chemotherapy pills, for example, like everolimus. So really, we have an arsenal of different drugs and how we make the decision is, ***what are our goals of treatment***? So, do we need to get hormone under control? Do we need to get tumor under control? What are the

various side effects of the treatment? How much shrinkage do we want to try to achieve? These are all the considerations when we're deciding on which treatment might be appropriate for a specific patient?

Lisa Yen:
Yeah. And that naturally leads me to wonder, there's all these different treatments that with the somatostatin analogues, lanreotide or octreotide, PRRT, everolimus and then, I'm sure there's other ones out there. What about sequencing of treatments? Does it matter? Is there one where if you start doing that, that will close the path for another one?

Dr. David Zhen:
It's a fantastic question. And I would say that's actually one of our leading questions nationally within the neuroendocrine field that we're trying to figure out. So, I think at this point in time in terms of our clinical practice, in terms of how we make decisions, it's just the factors that I discussed: patient preference, potential side effects, what are the potential response rates? In other words, if let's say, somebody has a very large tumor, and we really need to focus on getting shrinkage to make that patient feel better, some treatments have better response rates as compared to others. So, we make those decisions. And I think there's a preference a lot of times, for example, PRRT, we often do that a little bit earlier in the treatment just because patients tolerate that a little bit better. In some patients, they may get responses. But yeah, we don't really have great level one evidence or high-level evidence to know what is our optimal sequence and strategy.

I would say there's been a couple of studies now in pancreatic neuroendocrine tumors that were presented at one of the national conferences in Europe, the European Society of Medical Oncology, where they're actually starting to try to answer these questions. And the questions that were asked is, “Do we do medical therapy first? Or do we do PRRT first? And what are the outcomes?” And at least what we can say from those initial studies is that in pancreatic neuroendocrine tumors, in some situations, doing the PRRT may actually be a little bit better. But I think there were a lot of caveats to those studies, because they were comparing to treatments that we might not necessarily prefer in some of our patients. And there's other treatments that we might have used. And so yeah, and I think nationally, there's actually trials being run for the NCI that will ask the question, trying to better sequence. So, I think, you know, in the years to come, we'll have better data to help actually give stronger evidence to our patients to say, “Hey, we should be doing this first or second.” But for right now, I think a lot of it is based on knowing the patient's characteristics, patient's preferences, provider preferences.

Lisa Yen:
And then zooming out on the bigger picture wrapping and surgery. How would you also sequence that with the PRRT, somatostatin analogues…

David Zhen:
Yeah, I think for the most part, if we're able to do a complete resection, we ideally like to do a surgery if possible, because that is really the only potential opportunity or potential treatment modality that we're able to really completely get rid of or eradicate the tumors. So, if we're able to do that we can. Now there are some situations where even if we can't eradicate all things, there's some recent data and more evolving literature suggesting that even if you can't get rid of the cancer, sometimes debulking surgeries, and this is most relevant for, let's say, in the liver, if there's liver metastases, because what we worry about there is as the tumors grow, it might impact liver function. And we know that affects patients’ prognosis as a result. And what the literature has shown is that if you can debulk, in other words, get rid

of as much cancer as possible and use your definitions of 90% or more of the disease, because if you cut out portion of the liver, some of the normal liver can grow back. So, the idea is that if you do those kinds of surgeries that might make patients live longer or have a better survival. And so, when we're making these decisions, in terms of surgery and systemic treatments, in the patients that we know we can't get rid of the tumors, we have those discussions in our tumor board. So, if we have a young, healthy, fit patient, and they want to be aggressive, then sometimes we'll have that discussion, we'll review it in tumor board, and I'll ask our surgeons, "Hey, do you think we could do a debulking surgery?" even if we can't do it. And then what that allows me to do is then I can use my systemic treatments and medical treatments later on as well to that adds on potentially to keep their cancer under control and keep their lives going as well, too. Right? So that's how we might think about using those treatments together.

Lisa Yen:
That's helpful. And on the flip side, what if someone's told that they can't have surgery? Is it possible that they could later on have surgery or more than one surgery?

Dr David Zhen:
Yeah, it is definitely possible. And we definitely have had patients who've had multiple surgeries, obviously, depending on what was resected, how they recovered from the surgery depends on whether or not we can do even more surgeries down the road. So that's one consideration. But yeah, sometimes we might end up having to do multiple surgeries. But I think one of the things that we have to think about is, *what's the goal of our treatment?* So if the goal of the treatment is to try to eradicate or get rid of the cancer as much with the hope of prolonging survival, I think absolutely it makes sense to do that. Sometimes what I see is that let's say, if somebody has another tumor come back in many different places, and then we say, "Can we do another surgery?" I think it's reasonable to ask that question. But if the cancer came back in a relatively short period of time, it's kind of like, "Do we really need to do a big surgery?" What's our gain from there, right? Now, I do think it makes sense to let's say, do a second surgery. For example, in small bowel neuroendocrine tumors, we worry about bowel obstructions. So, the tumor comes back in an area of the bowel and what we know is that if we remove that tumor, we might prevent them from having a life-threatening bowel obstruction, even if we leave the rest of the disease behind, but it might improve their quality of life and it's worth doing, that's why I think it makes sense. So, I think, really, when we think about what the role of doing more surgeries or more aggressive surgeries is really thinking about are we trying to get rid of most disease to try to prolong survival, and then also quality of life standpoint. So, we can clearly see that we can benefit the patient from those two aspects then that's usually where we're making a determination about doing surgeries.

Lisa Yen:
Yeah. What a helpful guiding question, "*What is the goal of a treatment?*" So, there's all these options for small bowel NETs? How are these treatments for small bowel NETs different from other NETs?

Dr. David Zhen:
So, I would say for pancreatic neuroendocrine tumors, as I mentioned, there's other oral chemotherapy regimens. One that many people may know is capecitabine and temozolomide. That's an oral chemotherapy regimen in pancreatic neuroendocrine tumors. They have another FDA approved drug called sunitinib, which basically is a targeted agent trying to target the blood supply related to tumors. So, in a very layman's way of thinking about as choking off the blood supply to tumors. Now, those two regimens were primarily studied in pancreatic neuroendocrine tumors, and so we know that they potentially work. We don't have as strong evidence in small bowel neuroendocrine tumors. I will say though, in some situations even my own, if I don't really have a lot of great options, or if the tumor is

actually a little bit more aggressive. We know the faster growing tumors often respond to oral chemotherapy a little bit better. I have in *some* select situations consider those various treatments. Now coming down that way, even though that's kind of our standard paradigm right now, that doesn't mean that some of these agents won't have a benefit in small bowel neuroendocrine tumors.

That might lead to your follow up question you might have Lisa is, "What are some of the new drugs that we might think about?" And there's been several studies that have been dedicated to also including patients with small bowel neuroendocrine tumors. And I think what's coming down the pipeline that's somewhat exciting is one is, as I mentioned, sunitinib in pancreatic neuroendocrine tumors, is what we call VEGF targeting agents or targeting the blood supply. There's other agents that have been explored. And I think one exciting that's being explored is by Dr. Chan over at Dana Farber. She has a national trial that she's running looking a cabozantinib. It's another type of oral pill. And in that trial, what they're looking at pancreatic neuroendocrine tumors and small bowel neuroendocrine tumors, there are some preliminary evidence that might be effective, but we're waiting on this large trial to see if it's effective or not. And so, we'll wait to see the results from that.

And the other things that are coming down to block too that are exciting for other neuroendocrine tumors and also small bowel neuroendocrine tumors, we have new forms of radiation molecules for PRRT. The new kid around the block is what we call ***alpha emitters***. So, the idea here is that different radiation particles can penetrate the tumor in different ways. And alpha particles might actually have a better, straighter path into tumors. And so, they might be able to be more effective than our traditional PRRT. And at the Fred Hutch, and just like many other centers, we'll be opening those trials too. And then likewise, there's even some newer agents that are coming down the block that are kind of immunotherapy related. To date, the immunotherapy-like checkpoint inhibitors haven't really had a lot of benefit. But what the newer agents are doing is trying to really engage the tumor and engage the immune cells and have agents take both of the cells that come to directly with each other. This is what we call ***bi-specific antibodies***, where one part of the molecule is binding to the immune cells. One part is binding to tumor cells and try to bring them together a little bit closer. And so, I think those are some investigational agents that are looking there.

So, to get back to your original question, at least in terms of how they're different and that kind of thing. There are treatments that let's say there may be a little bit more for pancreatic neuroendocrine tumors. But I think what's exciting is what's coming down the pipeline, potentially for small bowel neuroendocrine tumors.

Lisa Yen:
Yeah, well, that is exciting and hopeful that there are more things coming down the pipeline. So, say you have someone was living with small bowel NET, they've had whether it's surgery or you start them on medical treatments. Now, how would you monitor them? What types of bloodwork or tests should be done and how often or what type of scans?

Dr. David Zhen:
So oftentimes, in terms of monitoring patients for tumor response, usually rely heavily on the scans. And so oftentimes, the really the mainstay scan that we find the most helpful is the CT [or] CAT scans. And again, these have to be done multi-phase to make sure that we're catching all the tumors. When question comes up in terms of DOTATATE PET scans, where we're looking at the hormone production, sometimes I often find providers liking to do DOTATATE PET scans frequently, which is not wrong, you can definitely monitor disease with DOTATATE PET scans. But I would say there's a little bit more cost

related to those scans, the logistics in terms of getting the radioactive dye. And a lot of times it doesn't necessarily add more information than a multi-phase scan. So oftentimes, I think the CAT scans are kind of our foundation. It's really kind of whether the questions, *"What are your goals?" "What are you trying to answer?"*

One is sometimes the CAT scans might suggest that maybe we're concerned that there's cancer that we're not clearly seeing. And sometimes we might want to do a better scan. And so sometimes the DOTATATE PET scans might help us. Likewise, there's MRIs, which are magnetic scans, and these are scans that are really good for looking at specific organs or tissues. And that's where sometimes, for example, in the liver, even a CAT scan or a DOTATATE PET scan might not pick up all the spots that we want to see. And knowing that information might not only be helpful to know what's going on with treatment, but also let's say if we're going to do a surgery, we want to know that we've seen all the tumors, and we know where we need to go to resect all those tumors. And so that's where the MRIs sometimes are also helpful for detecting. So, we use all these different types of scans. But really the foundation is the CAT scans.

And then in terms of the biomarkers, again I think there's a lot of controversy in terms of even checking them and how helpful they are. But we often do the scans every few months, initially. But if let's say somebody has a slow growing tumor, sometimes I start extending those scans out every six months. I even have some patients I'm doing just once a year now because they've been so stable for a period of time. So really, the guidance in terms of the frequency depends on how is the tumor acting, so if it's more slow growing, and you can definitely extend the frequency. If things are kind of changing or you're not sure and you want closer follow up, you may do it that way. So, the point with the bloodwork is that oftentimes we check the bloodwork that aligns with the scans as well.

Lisa Yen:
What I really appreciate is, not only are you very clear in explaining, for example, to have a CAT scan, but you're also showing us how you think and what is the question that needs The answer, like what are the goals of the treatment? How is the tumor acting, and that really helps empower the patient community to learn how to think about these things so that it's not just like, okay, I'm gonna take this drug, but start understanding the bigger picture.

Dr. David Zhen:
Absolutely. And I would say, that aspect, which is what I appreciate from all the patient advocacy groups, including LACNETS, is just empowering patients, because this is a very unique type of cancer and disease, and oftentimes not a lot of knowledge. And so, I often really love it when patients empower themselves, because they've even sometimes teach me about things too, that I haven't even thought about. So, it goes both ways.

Lisa Yen:
It goes both ways. And we really appreciate that. And so, I guess on that note, we'll just end… I know you've talked about exciting new treatments already with cabozantinib, the new forms of PRRT alpha emitters, and the bi-specific antibody. What advances or what new advances are you most excited about? And then what closing thoughts, words of hope would you like to share with the NET community?

Dr. David Zhen:

I think compared to when I was in training, which was not too long ago, so I admit that, things have changed a lot. What I think is really exciting is the hype and just the advocacy, both from patients and providers of neuroendocrine tumors in general. I truly do believe knowledge is power. And I think what's really great here is just the advocacy for neuroendocrine tumors. And I want patients to keep going with that. Because if we don't have that advocacy, we can't advance research because oftentimes, even when I sit on some of national committees, like with the National Cancer Institute, we often say, "These are rare diseases, it's hard to do trials." We don't see the patients and that kind of thing. But we *do* see the patients, it's just that when we think about from a big-scale thing, there may not be as common as other cancers. But when we keep thinking in that direction, nothing moves forward. And so, I think just the keeping the advocacy, I think that's what's exciting is that more awareness. People are just more aware of neuroendocrine tumors. And that increases knowledge. I think it increases clinical practice and makes us be better doctors, because now we're thinking, hey, maybe this patient has neuroendocrine tumor, we really need to think about this. So, I think that's what's exciting. And that naturally leads to just all the future research, thinking about new ideas of how we want to invest resources and to think about new drugs, new development. So, I think that's really the most exciting that I'm seeing, is just the hype and the news for neuroendocrine tumors.

Lisa Yen:
Thank you for those words of encouragement, for all you do to help empower patients to increase the awareness and knowledge and, and the work that you're doing to increase future treatments with the research you're doing as well.

Dr. David Zhen:
Of course, my pleasure.

Lisa Yen:
We're really grateful for all you do both in clinical practice research and for all you've done just sharing this knowledge, education, information and all that you do with the patient advocacy groups as a whole. Thank you so much again, and we look forward to seeing you again next time.

Dr. David Zhen:
Same here. Thank you for your time.

Lisa Yen:
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