“Key Considerations for NET Surgery”
with Dr. Alexandra Gangi
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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.

Welcome to the LACNETS Podcast. I'm really excited to introduce our special guest for today, Dr. Alexandra Gangi. Dr. Gangi is a board-certified surgeon and surgical oncologist at Cedars-Sinai Medical Center in Los Angeles. Dr. Gangi completed a general surgery residency at Cedar-Sinai and her surgical oncology fellowship at Moffitt Cancer Center in Tampa, Florida.

She currently serves as the Director of Gastrointestinal Tumor Program at Cedars-Sinai in Los Angeles, California. And she specializes in neuroendocrine tumors, metastatic and primary liver tumors, colorectal cancer, pancreatic cancer and management of peritoneal surface malignancies with cytoreduction and (HIPEC.) Dr. Gangi’s current research is focused on the understanding of tumor microenvironment and how it may cause disease progression in different sites such as liver, lymph nodes, etc. And she and her team are collecting tissue from primary and metastatic small bowel neuroendocrine tumors and sequencing to see differences in epigenetic signature in these tumors.

Dr. Gangi serves as the co-chair of the North American Neuroendocrine Tumor Society's (NANETS) Communication Committee, and she's a member of the organization's Diversity and Membership Committee. A couple of fun facts about Dr. Gangi—she speaks four languages, and she's raising a pandemic puppy named Charlotte.

Welcome Dr. Gangi. And I'd invite you to perhaps share how you got involved in the neuroendocrine community.

Dr. Alexandra Gangi:

Sure thing. Thank you, Lisa, for the very kind introduction and for having me today. So neuroendocrine tumors have always been an interest of mine from early training at Cedars-Sinai, we had a, and still have a, fairly robust neuroendocrine program and see a number of patients with different types of primary neuroendocrine tumors. And so early on as a resident in the OR, we certainly operated on a number of these patients, and it was just so different from some of the other cancers, and the way we manage other cancers.

In that for a majority of other malignancies, there's very specific algorithms that we follow, and you know, you're either eligible for something or you're not, and there's really no gray area. For patients with neuroendocrine tumors, there's a lot more room I think, and the treatment was just so individualized and came down to the specific patient, their particular tumor and where in their treatment journey they were. So, that was of tremendous interest to me. And so, I

got engaged early on, and it's continued to be kind of a passion of mine. And I absolutely love my NET patients. They're definitely the most unique in every way outside of just their tumors. So, I'm privileged and glad to be part of this community. And then I think the providers who treat NETs are also just some of the most fascinating and interesting people and kindhearted doctors that I've ever worked with. So, I think it definitely keeps us all engaged.

Lisa Yen:

We certainly have an amazing community of patients, caregivers and doctors, and I love seeing your face light up as you talk about them. And we're grateful that you're part of that community as well. So, let's jump into our 10 questions for today, shall we?

Dr. Alexandra Gangi:

Sure thing.

Lisa Yen:

So, our first question is, how do you decide if tumors can and should be cut out? I know, this is a big question, but this is a very common question as well. And how does tumor location, size, and the amount of tumors, factor in your decision?

Dr. Alexandra Gangi:

Yeah, I think that's an excellent question, obviously, then, like you said, it's a big topic and requires an entire conversation in and of itself. Especially if you find a surgeon who does this for a living, we have plenty to talk about. But I think to kind of give a broad picture, when we're first seeing a patient with a neuroendocrine tumor there's a few critical components that we want to evaluate.

One is where did that tumor come from? Where did it start? And is it still solely in that particular site? So, do you have a small bowel neuroendocrine tumor that's metastasized and where has it metastasized to? Has it metastasized to the liver? Has it gone outside of the liver, things of that variety? The second piece, or maybe the concomitant piece, is the grading and the aggressiveness of your tumor. So, we have, you know, a broad range of neuroendocrine neoplasms. And then we have neuroendocrine carcinomas, which are higher grade and kind of don't fit into the well-differentiated subtype of neuroendocrine tumors. So regardless of where the tumor may have started, and where it currently is, the treatment algorithm may be a little bit different, just based on the pathology. And I know there's certainly excellent talks out there that have been given in the past about understanding your pathology. And I think that's critical for neuroendocrine patients because it's so nuanced. There's just a lot to digest. So as a surgeon, those are the things you're looking for. What are we looking at, where is it from, and where has it gone if anywhere? And then the pathology of it.

So, if you have a single tumor, right, we know that you have a tumor in your small intestine, or let's say, your pancreas, or your colon, which is certainly more rare, and it has not metastasized anywhere else, then the decision typically is to remove that tumor regardless of its size. Sometimes in a pancreas tumor, if it's very, very large, or encroaching on multiple different things, we may want to give you some treatment first to shrink it, because that makes the surgery simpler sometimes. And we can spare some important organs. But in a non-metastatic tumor that's removable, the mainstay of treatment is surgery first, typically.

If you have metastatic disease, that then becomes a little bit more confusing because there's many different ways that that can go. So, some patients will have metastatic disease from their primary site frequently to their liver only. And if you have liver only disease, then that opens up a whole other slew of treatment options that are available for you in which surgery is actually included. The concern there is sometimes we have kind of different classifications of patients who have tumors in their liver. Sometimes you have multiple tumors throughout the liver, and they might be very small, but you have too many of them. And so to go in then and cut them out would make your liver look like a really bad piece of Swiss cheese. And it's just not feasible, or beneficial, because we always are concerned that there's probably tumors in the liver that we just can't see at the cellular level. And so, we put you through this whole big operation, and they might come back.

Alternatively, you have some patients who may have two or three very large tumors in their liver, that are amenable to having them removed surgically, especially if we're going in simultaneously to also remove their primary tumor. If you develop liver metastases after surgery, or the first time we're meeting you, you've had surgery 10 years ago, and now you present with liver metastases, then we kind of go through the different treatment options with you. And surgery may be one of them. But it kind of has to be catered specifically to your case. And again, we go back to pathology, how long you've been with or without the liver disease, your overall health, your symptoms. So there's a lot of factors to consider. And I think just like there's some good pathology talks there, certainly some really good talks about when to consider surgery. And that's where the tumor size and the number of tumors kind of will factor into the decision-making process.

And then the tumor location piece, like I said, it just depends on if it's the sole site of disease, or if it's metastatic. And then sometimes tumors may present in areas that are just not favorable for resection. Because, for example, you may have a liver tumor that's sitting right smack dab in the middle of your liver and to cut it out I either have to cut out half your liver in one direction or the other and for a one-centimeter tumor, you know, that doesn't make sense. And so sometimes we use alternative therapies for that. So, location does matter. Similarly, for pancreas tumors, sometimes if they're in the mid body versus the head or the tail, or how close they are to a duct that may make the difference between the need to remove part of the pancreas, all of the pancreas or just kind of pull that particular tumor out with an enucleation. That was a very laborious answer. But hopefully, hopefully it gets to the point – it's not straightforward and it's not a "one size fits all" thing.

So, although you may meet a patient who also has had neuroendocrine cancer, and they'll say, 'well I had surgery, and this happened,' that may absolutely not apply to you. So, it's really important to see a surgeon, to have an evaluation, to make sure that, you know, we see your scans and then for you to kind of understand the rationale of why we want or don't want to do something.

Lisa Yen:

Yeah, what an amazing amount of planning and thoughtfulness goes into the decision. Thank you for that. That's really incredible to just hear you discuss that and, and really see how important it is to see a surgeon and have that really thorough discussion about it. The next question would be, how do you decide if someone should have a laparoscopic surgery versus an open surgery? We know you do both. And also, what about robotic surgery?

Dr. Alexandra Gangi:

Yeah, absolutely. So certainly, minimally invasive surgery, I'm just gonna lump that as one because it's laparoscopic and robotic. And depending on the day, your surgeon may have access to one and not the other. So those are things that patients don't always consider, but it basically means surgery with smaller incisions. It's certainly feasible for neuroendocrine tumors. And I think we typically will consider doing that when we feel as though we can do it safely and just as well as we can do it open.

In terms of my considerations for doing something lap, robotic, or open, it basically comes down to a few things. What am I operating on? And then am I operating in multiple different sites in the body, like am I operating all the way down in your pelvis and then all the way back up in your liver? Am I taking out tumors that are very large? Am I taking out a whole chunk of tumor, or like a big piece of liver that I'm going to have to make an incision for to remove anyways? Because I'm not going to save you anything by, you know, making four little incisions and then adding the big incision afterwards. That kind of doesn't make sense.

And then with respect to primary site for patients who have small bowel neuroendocrine tumors, our management approach is still that we have to palpate the small intestine. So, we know that about 30 to 45% of patients when diagnosed with a small bowel neuroendocrine tumor may have multi-focal disease. When I take pictures of these for the patients that I've operated on, because they never believe me, but honestly, I have found tumors and felt them with my fingers. And they're like, no bigger than, you know, two-three millimeters, they're teeny-tiny.

When we do robotic surgery, we have absolutely no haptic feedback. So, everything is visual, we can't actually feel anything, you can see that you're holding something firm, because the grasper won't necessarily compress and soften the tissue. And so, you kind of have this visual haptic feedback but it's not the same tactile feedback that you have with your hands. Laparoscopically, you're also missing some of that tactile feedback, but to a lesser degree. So, because of the possibility of having multifocal disease within the small bowel, for those cases, I'll typically approach it as a laparoscopic or robotic assisted, meaning we'll go and make some small incisions, kind of run the bowel visually to identify where the primary tumor might be. And then we typically can make a three-to-seven-centimeter incision depending on the patient's body habitus, how tall they are, and how much fluffiness they have. I certainly have my own fair share. So, then we make essentially a small incision, we can bring out the bowel and basically feel almost all of it and we run the bowel two or three times and identify, and you know make sure, we only have tumor in the area that we'll be taking out. So, for that one, it's still recommended to have at least an open component.

For liver, pancreas, and rectal, a bulk of the time, you can do these minimally invasively or robotically, but again, if I'm taking out, and I've done this, taking out, you know, half the left lobe because there's a 12-centimeter tumor, and I have to take it out of you somewhere, that's pretty much the size of the incision, I need to do the surgery anyway, so it doesn't make a difference in terms of the patient's recovery. But those are the considerations.

Lisa Yen:

It's helpful to know, I know, while most patients would rather have smaller cuts and better recovery, it's helpful to know what's running through your mind as you're making that decision and why it's worthwhile to have a bigger cut. So, the next question, especially those with small bowel NETs, they hear this word ileocecal valve, so how do you decide whether or not to remove the ileocecal valve and if you could first kind of explain what that is?

Dr. Alexandra Gangi:

Sure. So, the ileocecal valve is essentially a valve-ish, that sits between the small intestine and the entry point into the right colon. The thought there is that once stuff has passed through the small intestine into the right colon, you don't really want it refluxing back into the small intestine. So, it's kind of a one-way valve to prevent stuff from going backwards. What you have to understand is at that point though in your body, the stuff that's going into your colon is not the same thing that you see when you go to the bathroom. It's essentially still very, very, very, very liquidy. And the fluid hasn't really been reabsorbed out of the system. So, it's basically a reflux of fluid that would be going backwards.

Some patients have an incompetent ileocecal valve, meaning it doesn't work, but they would never actually know it unless they developed an obstruction you may have issues with. Because things do reflux, you may actually have worse symptoms than someone who has a competent ileocecal valve who would then present with something like a large bowel obstruction and a lot of stool. I have and have not removed ileocecal valves in different patients depending on where their tumors are, and I can tell you from a recovery perspective, you would never know it. I have not seen higher rates of bowel movements, or discomfort, or ability to tolerate food or anything else that varies between someone who undergoes an ileocecectomy (meaning I would take a part of the ilium and part of the cecum), which is right where this ileocecal valve sits, as compared to someone who's had just a small bowel resection or right hemicolectomy. So, I know although we talk about it, I don't know what value it actually has post-surgery.

So, I would recommend that if you are concerned about losing that valve, there are other ones that you should be much more concerned about than this one. So it's not as critically important to you or your well-being. If we can, more importantly, I think it's preservation of the ileum. A lot of these small bowel neuroendocrine tumors are found in the distal ileum, which is the third part of the small intestine. So, it's broken up into three parts, the duodenum, which hugs the pancreas, the jejunum, which kind of is the whole mid part, and then the ileum is the last part right before it goes into the colon. And incidentally, we find a majority of neuroendocrine tumors in the ileum. And the ileum is responsible for absorption of some nutrients and then production of some factors that help you reabsorb B12 and also reabsorption of bile salts. So, bile salts essentially help you with not having floaty and frequent bowel movements sometimes. So, when we're removing a lot of ileum that's a time in which we see patients may have sometimes difficulty with

absorption of fatty foods and things of that variety. That I think is much more important consideration, when speaking to your surgeon than having a competent ileocecal valve or not. So even if we're able to preserve five to ten centimeters of ileum, typically those symptoms will be significantly less as compared to in patients in whom we've had to take significant portions of the ileum.

Lisa Yen:

That's reassuring to hear. Thank you for that. So, as you know, many NET patients are evaluated for surgery. And as they look forward to surgery, what workup should NET patients have before their surgery? And should all of them have an echo done?

Dr. Alexandra Gangi:

So, I'm going to take this kind of one step backwards and just say any patient, forget NET patients before surgery, what workup should they have, it all comes down to, honestly to a degree, it comes down to your overall health and your age. A majority of hospitals have very specific criteria in terms of what they require. Once you're past a certain age, you know, over 45, everyone needs an echocardiogram, not an echocardiogram, I'm sorry, an EKG. Not a formal echocardiogram like you've asked, but an electrocardiogram, and some blood work and things of that variety to make sure they're sufficiently healthy and there's no gross abnormalities within their potassium or sodium levels. Other patients who are a little bit older, have cardiac risk factors, have a history of myocardial infarctions, things of that variety, all of those patients would be getting echoes and evaluations from cardiologists. Potentially, some patients who were undergoing very big operations will get stress tests, if deemed necessary by their cardiologist. So that kind of applies to everyone broadly.

With respect to NET patients, I think to a degree, they still fit into that. For patients who have neuroendocrine tumors that are functional, meaning they have actual symptoms. And essentially, when we're talking about symptoms, frequently, we're talking about carcinoid symptoms, which will include episodes of flushing, frequent bowel movements, sometimes rapid heart rate that we call tachycardia, or sometimes feeling like you can't really get a deep breath in because you get something called bronchospasm. Those patients, because they are kind of over-producing hormone, have a risk of developing secondary cardiac issues known as carcinoid heart disease. And we typically, in patients who have any of those risk factors or do have symptoms, we'll frequently check some bloodwork, serotonin levels, 5-HIAA levels. And if those continue to go up, you typically get a baseline echo when we first meet you typically, that'll happen, so that we kind of have an understanding of what your heart function is. And in many patients, your function may be entirely normal, and you just have the carcinoid symptoms.

In patients who then have carcinoid heart disease who are undergoing surgery, it's definitely necessary to have an echo before surgery. And sometimes we'll find that patients actually need to have management of their cardiac issues and cardiac valve surgery before they can undergo either an operation or a procedure. If you don't have symptoms, and you're otherwise healthy, and your 5-HIAA and serotonin levels are normal, and we have no concern that you have carcinoid heart and you know, you're within the right age frame, and you've seen your primary care doctor and they feel as though you're sufficiently fit, you don't necessarily need to have an echocardiogram in preparation for surgery. So, lots of different things to kind of consider within the checklist, but it's not an automatic "I have neuroendocrine tumor, therefore I need an echo."

Lisa Yen:

Yeah, that's really helpful to hear. And just out of curiosity, how recent of an echo or EKG would you need if you're getting those studies done?

Dr. Alexandra Gangi:

So typically, we'll do it depending on the severity of disease, like sometimes, you know, we'll do it annually. Other times, if we see that there's worsening function, we may start to do it more frequently, at six months. If we do know that you have a history of carcinoid heart, or that you're at high risk, we typically want an echo within three months of surgery. I

typically will order close to your operative date so that we don't have something old to work on. Certainly, if we've done something three months ago, and then you're developing new symptoms, because you'll see your surgeon before surgery, like if all of a sudden, you're saying like oh, I can't lay flat when I sleep, and you know, I can't do these things or look at how swollen my legs are, then that would require that we re-work you up, which is why it's kind of important. So, the timing is not, not definitive, and can vary depending on what's going on with you.

Lisa Yen:

And speaking of carcinoid symptoms, that's good segue to the next question, what is the risk of carcinoid crisis with surgery, of course, biopsy and also even a dental procedure and how would you manage this?

Dr. Alexandra Gangi:

So, for patients who have nonfunctional tumors, meaning as far as we know, you haven't had any symptoms of the ones I mentioned, the carcinoid syndromes, you have a nonfunctional tumor, because there's also tumors that are functional, not necessarily manifesting as a carcinoid crisis or carcinoid symptoms. We typically are less concerned about you developing any type of carcinoid crisis symptoms. And just to be clear, carcinoid crisis refers to when you're having these procedures, or you're manipulating tumors or poking them or doing other things, you have an over release of hormone, which can then lead to very labile blood pressure. So, some patients have a significant drop, other patients will have a significant increase, the difficulty breathing that I mentioned, you could see flushing and just huge variations in all kinds of hemodynamic parameters in the patient. That's kind of what we're talking about when we talk about crisis. And when we're doing this at the time of surgery, if we have someone who's symptomatic, who has carcinoid symptoms, we typically recommend that those patients will get some somatostatin analogs before the actual surgery, like their monthly injections, because that does help actually limit the over production of hormones with stimulation. But at the same time, we have specific anesthesiologists with whom we work, who have an armamentarium of medications and are prepared to administer them to manage the changes in your breathing, or blood pressure, or whatever else.

So, during surgery, it certainly can be concerning, but it's less of an issue, because you're typically intubated when we're operating on you. We have control of your airway, we have control of your heart, we kind of have control of things, we have a team there who's available and ready to do all of this stuff. With a biopsy sometimes you know you have limited resources. So, it's important when you're having a biopsy, if you do have carcinoid symptoms, to tell the proceduralist, “Hey, this is you know, I've been told this is what's going on. This is the last time I had my somatostatin analog shot. I have a pen available with me, if anything were to happen, so that your entire team was aware.”

Similarly, with a dental procedure, you just want to make sure that you've alerted both the dentist that if you are taking somatostatin analogs, that you have a pen with you available, because sometimes there's just no rhyme or reason in terms of how or why you may react. It is really uncommon for a patient who does not have carcinoid symptoms to go into a carcinoid crisis. I'm not saying it's impossible, sometimes you may not even know that you have occasional episodes of flushing. So, you may actually have carcinoid symptoms, you just don't know it because you're not sitting in front of a mirror for 24 hours a day and don't see that happening or don't feel the overwhelming kind of heat rush that comes on. And so again, not impossible, but unlikely if you don't have known carcinoid crisis that any of this can happen.

Lisa Yen:

So helpful and reassuring. And you already touched on the next question about should NET patients be on somatostatin analogs before surgery? Feel free to expound on that. And also, what about after surgery? And if you start it after surgery, when should you restart it?

Dr. Alexandra Gangi:

So typically, for our patients who have carcinoid symptoms, we recommend the initiation of somatostatin, certainly as early as feasible. Some patients don't like taking medication, some people don't like, you know, shots. There's sometimes difficulty with authorizations, cost – I mean, there's a whole slew of reasons as to why someone may not actually initiate somatostatin analog therapy. But we do think that there is a benefit in patients who have symptoms in

terms of control of symptoms. And certainly, before surgery, I do prefer that a majority of my patients do go on it, because I found that there's certainly less concern and less variation in terms of how the patients do at the time of surgery with manipulation. With respect to should all patients be on it, again I think if you have no symptoms, and you have non-metastatic disease, right, there's really no indication for you to be on a somatostatin analog. Additionally, if you have the variant of a neuroendocrine tumor that does not light up on a DOTATATE scan, or somatostatin [scan], you just don't have the receptors. So again, giving you that medication is probably a limited benefit. That's a small subset of patients, but it just doesn't necessarily apply to you. And then after surgery, typically, we will recommend continuing on somatostatin analog therapy, at our institution, for about a year if you've had metastatic disease.

Now, some patients just don't tolerate somatostatin analog therapy well, and that's an entirely different discussion. But we do find that it is beneficial, it is supposed to be cytostatic, meaning it's supposed to prevent additional growth of tumors, it's not going to make anything shrink. So, when we're asking you to take somatostatin analog before surgery, it has nothing to do with tumor shrinkage. That might be the case when we're asking you to take chemotherapy or have some other kind of intervention. But I also think that's an important nuance.

Lisa Yen:

Yeah, as you said earlier, there's no “one size fits all” and it really depends on multiple things. And there's a lot of thoughtfulness around this as well. You mentioned chemotherapy. So, when would you want someone on chemotherapy or PRRT to shrink the tumor before surgery? And when might you want to do surgery first, followed by another treatment.

Dr. Alexandra Gangi:

So, I think, again, this comes down to if we're looking at a singular tumor, the size of that tumor and the proximity to other important things. So, you know, frequently I'll talk about the pancreas, the grading of the pancreatic tumor, if it's something that looks as though it has a higher proliferative index, meaning a higher Ki-67 or mitotic rate, and it's very sizable, and we can get it to kind of shrink so that that would change the operation. That's an option. There's some chemotherapies that are easier to tolerate versus others. There's some that we know work really well to shrink things quickly, but then they don't keep doing a really good job afterwards. So sometimes we'll give you one of those drugs to get maximal shrinkage really, really quickly before surgery and then take you to surgery to do the least aggressive surgical approach. But that chemotherapy wouldn't have been something that we necessarily would want you on long term because it's actually difficult to tolerate.

If we're looking at kind of multi-site disease, so let's say you have a tumor in your pancreas *and* your liver, a lot of times we will do chemotherapy first, at our institution, just to kind of get some understanding of disease control and disease biology, make sure that you respond to this treatment. It also allows us to determine if it's a good therapy for you after we do the surgery, because we can look at the pathology and if it looks like things shrunk and died, that means, hey, that chemotherapy was really helpful and they can keep you on it.

With respect to small bowel tumors that are metastatic, there is no good chemotherapy for those tumor types. So frequently, we favor either a combined surgical approach with maximal debulking to 70 to 90% if you have multi-site disease, that's resectable. Alternatively, you might use multimodal therapy. So you may use liver directed therapies and surgery to remove everything. And then if you have disease outside the liver, outside the liver and the abdominal cavity, then sometimes we may consider something like PRRT as a systemic therapy.

When do we want to do surgery first, followed by another treatment? Again, it depends entirely on the case. This isn't a topic of interest currently with respect to PRRT specifically, because we do think PRRT might work a little bit better in tumors that are smaller. So one question is in patients who have, let's say, really large, bulky metastatic tumors in their liver, is there a benefit in removing those guys first before you get PRRT, so that the PRRT could be more efficacious. And we have seen sometimes in patients who have gotten PRRT first and gone to surgery, and they're having small bowel surgery, there's sometimes this kind of worsening fibrotic reaction around the root of the mesentery, which is typically where you have the bulky lymph nodes. And sometimes those surgeries are actually more difficult. So, I think we need

certainly additional data. Because if you think about it, PRRT is still fairly new in the armamentarium of things that we've used. And the sequencing of where does it fit pre-or-post surgery is something that's still being outlined, but there should be some exciting trials and new data that will be arising in the near future.

Lisa Yen:

So, stay tuned for more – more work and more data. Well, so after surgery, of course you do so many of these, and you want to get people to the other side. So, after surgery, when would you recommend imaging of a patient? And then what type of imaging would you order?

Dr. Alexandra Gangi:

So, again, I keep thinking this topic broadly. Because I go back to like, there's so many different subtypes of neuroendocrine tumors and where they start and where they come from and where they're going. So, the imaging may vary based on that the timing may vary based on that. It's funny, because I think in 2017, there was an article published in JAMA [Journal of the American Medical Association]. And I was so excited when I saw the title, and it said, I think it was something like, '*Guidelines for Imaging Patients with Neuroendocrine Tumors*.' And I was like, yes! Finally. A guideline – something I could just follow! And it literally just said, you know, there's no perfect algorithm, and you should just keep doing what you're doing. And it's like, well, that doesn't help me at all.

So, I think it just comes down to sole site of disease, status post resection, typically the first imaging will be at six months. Unless there's a reason to image you sooner, meaning like you're coming in with weird abdominal pain, or obstructive symptoms or something else. It's not because we're worried about tumor recurrence, it's because you just had surgery and something is not right.

So, things may not be sitting the right way, we'll do it sooner. But from a cancer only perspective, if we've cut everything out, you didn't have metastatic disease, six months. Typically, for me, if you have metastatic disease, I will first image you at three months post op. And that's primarily because I just want to have eyes, primarily, especially in the liver, because we know we're always concerned. So when I'm doing liver surgery in patients with metastatic NETs, I give them an 85% chance of recurrence within the liver at five years. Meaning, there's a high likelihood that something is going to come back within the next five years. So, the sooner I see it, the quicker we can act on that particular change. And so I'll typically do a repeat scan after three months. Sometimes when we're doing the liver surgery, we'll also do liver ablations, depending on where the tumors are, if they're deeper in the liver, and we can't get to them, and they're teeny-tiny, like a centimeter or something like that. If we image you too quickly, it just looks like those who've grown and you then don't know what to do with that. So sometimes you want the inflammation to die down.

And typically to look at the liver, and MRI is preferable to a CT scan just because it's a little bit more sensitive. And the thing that's actually critically important is the type of scan you get for the liver needs to be a multi-phase scan. So neuroendocrine tumors that metastasized to the liver are fed by the arteries, which is why patients with NET tumors are eligible for all these arterial therapies. But you have to have basically a contrast injection, whether you're getting a CT or an MRI, that specifically shows those tumors lighting up on the arterial phase. And that's how we can determine if something is still maybe alive after an ablation versus not, and it allows us to see potentially new tumors.

So, MRIs are sometimes difficult to tolerate for patients. A lot of people are claustrophobic so I don't do that every three months, but at least annually, we'll do an MRI in our liver metastatic patients, but three-to-six months for everyone else with some kind of imaging via CT or MRI. And then if you don't have metastatic disease to your chest, we typically won't do a chest CT. Lung metastases are not common. But you know, they certainly can't exist. But we do have primary lung mets, which I'm not even talking about, because that's not my area at all.

And then Gallium scans, we typically will not do on a routine basis, unless we see either some kind of symptomatic changes that you're having and we're not able to see anything on any scan. Sometimes patients will have very, very small bony metastases or other metastases that are just too small for us to be able to see on an MR or a CT, that will be picked up by a Gallium, so that's an indication. If we're seeing something where we're not sure if it's residual disease,

new disease, or what it is specifically, and then if we're evaluating you for PRRT treatment. Those are the standard times to do the Gallium scan outside of your initial diagnostic Gallium. So, people will frequently say like, okay, so when are we getting another Gallium? And it's like, well no, we're not anytime soon because you don't need one. But that's essentially the algorithm, given the lack of an algorithm.

Lisa Yen:

Well, what really stands out to me is, especially you mentioned, for metastatic disease, the 85% recurrence rate, what stands out is that you have this cautious optimism, you're not just like, oh, I'm done, but really keeping people on a short leash, and trying to stay ahead of it. And really caring for people for quite a while. So, I'm also curious, how long do follow patients after you operate on them?

Dr. Alexandra Gangi:

If it was up to me and follow them forever because I love them. Definitely five years. And for my younger patients, I mean, I think it's just that question, we just don't have good data. And we know that these are slow growing tumors. So sometimes, you know, after you've gone out five years, which is what we do for a majority of other cancers, we have patients who recur 10 years down the line, it's just a question of, okay, should we be scanning you annually? And that's typically what happens. So, we'll still follow up. So, I kind of favor the 10-year plan. Which, of course life changes, and people move. And you know, fortunately, we have a close-knit community, and then we just refer them to another colleague in a different state, but definitely over five to ten years, no question.

Lisa Yen:

So, you have long relationships with your patients, you can see them grow up and go through life changes. And…

Dr. Alexandra Gangi:

I think that's one of the first things I tell my patients, I'm like, you know, if you don't like me, that's okay, we have to find you someone you like because you're going to be stuck with this person for a little bit of time. So, make sure you, when you have neuroendocrine tumor, make sure you like your team because they're going to be with you for a bit.

Lisa Yen:

And that's also really comforting to know that you're going to be there for them. Well, second to last question, as you know, many people go and get different opinions, especially because there's a whole push to see NET experts. So, if they see multiple people, why are there differing opinions from that specialist, specifically about surgery, and also, what treatment should be offered as a next option.

Dr. Alexandra Gangi:

Right. So, I think the reason there's different opinions is because, again, there's no standard approach. And typically, we use our collective knowledge of what we've done before and what has seemed to work well, and tend to apply that. I think different neuroendocrine tumor surgeons have different levels of comfort in doing particular things. And I think all of us are certainly always providing an opinion based on what we think would be best for you, and depending also on the additional treatment options that we may have at our institution that would be available to you.

So, I think if someone is in a location or institution where they don't have PRRT or you know, a strong IR team, they may not say that that's a good option, because it just realistically may not be for that particular patient at that time. Then alternatively, if that's the way things have been managed at that particular institution, and then surgery is secondary, that might be what fits into their treatment. It's not that it's wrong. It's just a difference of opinion, which is why I think it's important to get opinions. I think where it can get confusing is if every person you're seeing is giving you a completely different opinion, then you really just don't know what to do.

So I mean, I try to approach it in a way where I try to explain my rationale in terms of what I'm thinking and why. And then I will frequently leave it to the patient and say, you know, if I feel strongly about something, I'll say, I really think

that you need to do this. If, however, I think that two things could be potentially equivalent, and one doesn't take away from the other in terms of the sequence, then I'll say we can approach it one of two ways. And either one does not take the other option off the table down the line, and kind of allow the patients to sit with that and think through it and decide what they would want done next.

You have to keep in mind that a lot of times because these tumors can be slow growing, and because the disease progresses kind of over time, and takes pauses at random points and goes to different places at random points. Sometimes you're just "procedured out." So you know the patient may be coming to meet a surgeon, you as the surgeon for the first or second time but you have to look back and say like, okay, this person, this person's like, been through the gauntlet of surgery. And maybe even though I think this is the best thing, it just doesn't make sense. So I think you have to provide that alternative opinion and understand where they're coming from and make sure that it's a patient- centered decision. Sometimes there are no other options. Like, if you have a primary tumor that needs to come out, I'm going to tell you, it needs to come out, you know, we're not going to do anything else. But, so get opinions, but don't overwhelm yourself by getting too many, because then it can sometimes just get a little bit confusing.

Lisa Yen:

Yeah, that's helpful piece of advice. And also, I really like how you weigh in the patient in the discussion, and really what matters to them and having a discussion about it. So, the last question is, what questions would you recommend that patients ask at their surgical consultation?

Dr. Alexandra Gangi:

Yeah, so I think again it depends on the patient and what they're coming in with. One, I would ask broadly about the different options, even if you have primary site of disease in the small bowel or the pancreas, and we're saying do surgery, you know, it's an important question to say, okay, "What are my other options?" And there may not be any, but I think you need to ask that question.

And then secondarily, the question I always get asked is, "What would you do if I was your family?" And I, I can say the same exact answer. I think it's funny that patients think like, we would recommend something entirely different to a family member than we do to them. That kind of makes me sad, really about the whole profession, that were viewed that way. But I do think it's a good question, because it brings everything back down to the root to say like, okay, "Well, what would you do if this is someone that you really cared for? What would you tell him to do?"

And then I think, sometimes if you don't feel entirely comfortable with what's been recommended, I would ask the doctor directly, like, "If I were to get another opinion, is there someone that you would recommend talking to?" Because, I mean, we all know and like each other, for the most part, just kidding - we know and like each other, not for the most part, but definitely. But sometimes it's helpful to just get an idea of, don't necessarily go out and find someone on your own who is a self-proclaimed NET expert, maybe just ask one of us so that we can tell you to go talk to doctor so-and-so that they can give you their totally unbiased opinion as well.

I would ask about what to expect immediately before surgery. So, sometimes you have to do a bowel prep, other times you don't. What the downtime will be and what is the duration of time that will be in hospital? How soon can I expect to return to normal activity? I think that question, it's important for your surgeon to ask you what is normal activity, because for some people, it's like they're a tennis pro, and you're like, okay, that might be a little bit longer than a person who just wants to walk up their stairs. So, you have to define normal activity, what a rational number of time would be to take off work, expectations post op, meaning what can I expect, if I'm taking out, you know, half your pancreas, we could talk about malabsorption syndromes. And if you're going to need to be on medication, similarly with your small intestine, how that's going to affect potentially your activities of daily living. Because some people, for example, need to be on the road, that's their job. And if I say, well, you may have to go to the bathroom anywhere between three and six times a day for the first few months after surgery until we get this situated. Well, that may require that they take additional time or let their employers know.

So, all of those sorts of things, both cancer specific things and then surgery specific things. And then typically, we'll have a conversation about how they can best get ready for surgery. And I recommend that everyone try to walk one to two hours a day, eat right, do all the things that are healthy, because the healthier you come in for surgery, the faster you recover, invariably, and the faster you go home, just because you have a lot more reserve. So, if someone is like really malnourished or just barely able to take a couple steps in either direction, our surgeon may actually say, I don't think you're sufficiently fit to have an operation just because I'm worried about your recovery on the back end. So those are all important components.

Lisa Yen:

Those are excellent practical tips. And I imagine really helpful for patients that focus on right getting stronger for surgery, it's not something passive, it's something that they can do something towards. So, as we close, I just invite you to share any closing thoughts, comments, anything you'd like the NET community to know or any particular words of hope?

Dr. Alexandra Gangi:

I think the words of hope are you have a group of physicians and researchers and patient advocates who are really motivated to empower you and inform you, and take treatment for neuroendocrine tumors to the next level, so to speak. I think there's a lot of different treatment options that are in the pipeline. I think us understanding the different algorithms of how we should manage patients is continually evolving. And I think there's just a really motivated group of people who are really interested in, in neuroendocrine tumor. So, in that way, I hope that gives you some peace when given this diagnosis, that there's an entire community out there backing you up and hoping to do the best thing for you. And I'm thrilled to be a part of it and certainly if I can be of any help, Lisa knows how to find me. So, hopefully that that helps to a degree.

Lisa Yen:

Thank you so much for being part of this amazing community for your dedication, hard work, research, all the patient care that you provide and all the compassion. It's just really amazing to me how you work so tirelessly and you're so committed to our community. So, we're really grateful to have you. It's been a pleasure talking to you today and we look forward to connecting soon again in person.

Dr. Alexandra Gangi:

Thank you so much, Lisa.

Lisa Yen:

Thanks for listening to the LACNETS Podcast. We want to thank our podcast supporters Ipsen, Advanced Accelerator Applications, TerSera Therapeutics, and Lantheus. For more information about neuroendocrine cancer, go to www.lacnets.org.