THE LACNETS PODCAST

With Gary Ulaner, MD
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**Transcription:**

**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 excited to introduce Dr. Gary Ulaner, who joins us from Southern California to discuss the imaging of NETs. Dr. Ulaner is the James and Pamela Musee Endowed Chair of Molecular Imaging and Therapy at the HOAG family Cancer Institute. He is the Professor of Radiology and Translational Genomics at the Keck School of Medicine University of Southern California. Dr. Ulaner was previously with Memorial Sloan Kettering Cancer Center where he trained under Dr. Lisa Bodei who is well known to us here at LACNETS. Dr. Ulaner are served as the PET CT expert on the breast cancer disease management team. Dual-board certified in radiology and nuclear medicine, Dr. Ulaner is a nationally recognized expert in the use of targeted imaging to help direct focused cancer therapies. Dr. Ulaner completed his medical degree and a PhD in cancer biology at Stanford University School of Medicine, an internship at Johns Hopkins Hospital and his radiology and nuclear medicine residencies at the University of Southern California. A fun fact about Dr. Ulaner is that he is a competitive west coast swing dancer. How cool is that? Welcome, Dr. Ulaner! We are excited to have you here with us today!

**Dr. Gary Ulaner**
Thank you so much for the introduction, Lisa. And yeah, west coast swing is the state dance of California. Go ahead and Google and look it up. Absolutely phenomenal dance. And I have to say, I'm so excited to be here today because my six year old son, Ilia, listens to podcasts of Neil deGrasse Tyson of StarTalk. And I'm so I'm just thrilled to be able to tell him that I'm doing a podcast like his favorite person now.

**Lisa Yen**
That's awesome! So now you're going to elevate your level of coolness in his eyes.

**Dr. Gary Ulaner**
We shall see, we shall see.

**Lisa Yen**
Okay, well, in our podcast, it is kind of cool, because we are tackling 10 the top questions in your field of expertise. So as we know, you're an expert in many things, but diagnostic imaging is one of them. And there's many questions that our population and our listeners have in this area. So let's first tackle this area of functional imaging. Our first question for you today is, what is the difference between a DOTATATE PET/CT scan and a FDG PET scan, or the type of PET scans that are commonly ordered for other types of cancers?

**Dr. Gary Ulaner**
Let me start by saying there's a difference between functional imaging and anatomic imaging. Anatomic imaging would be seeing structures, it's kind of like you look out the window and you see a tree and it will have roots under the ground and it will have a trunk and it has leaves and flowers. So when you do anatomic imaging, you're looking at those individual structures. And those things could be CT scans, or MR scans, ultrasound scans, different ways of looking at that anatomy. Now, a functional scan tells you what's happening inside those structures. So when you look at a tree, you can't see that there's constantly photosynthesis occurring within leaves. You can't see that there's constantly water being drawn up through the roots and evaporating through the leaves. So a tree that's alive, and a tree that just recently died look exactly the same on anatomic imaging, whereas it looks entirely different if you were doing like a functional imaging of what's happening in water or oxygen or molecules within the tree. The same thing within the human body. Anatomic imaging, we can do a CT scan or an MR scan in order to say this is the liver. This is the lung. These are the bones. And be able to look for abnormalities within the liver and the lungs of bones masses. But functional imaging, allows you to see what's happening in those organs, what's happening in those masses. Because a mass that represents a treated tumor could look absolutely the same as an active growing tumor on anatomic imaging. Functional imaging scans allow you to say, ah, this is a living tumor that needs to be dealt with, versus this is already treated and dead tumor, which is no longer a danger to you. So in the category of functional imaging, the most common PET scan is called an FDG or fluorodeoxyglucose PET scan. And this is a radio-labeled sugar molecule. Lots of tumors like to eat sugar. Neuroendocrine tumors eat sugar, particularly if they're poorly-differentiated. So we can see neuroendocrine tumors and we can see how active they are by using an FDG PET scan. Now there's something also called a DOTATATE PET scan. This is a different type of PET scan that looks for something called a somatostatin receptor. So neuroendocrine tumors express different types of somatostatin receptors, and the DOTATATE binds to that somatostatin receptor, and then shows us where the somatostatin receptor is present within the body. For example, that anatomic imaging like a CT scan, if I see a mass in the liver, and then we do the DOTATATE PET scan in January, we can see that that tumor expresses lots of somatostatin receptors. Then the patient gets treatment in February, and then we repeat the scans in March. The CT scan may show very little difference, but the DOTATATE PET scan can show you, ah, all the cancer cells have been killed. Because the somatostatin receptors are no longer expressed. There's still a mass, but it's not living metabolizing tumor cells in that mass anymore. So often, these functional imaging scans provide much more important information than anatomic imaging scans. And perhaps the best is when you combine anatomic imaging together with functional imaging in order to get the best answers. So when we say someone has a DOTATATE PET CT, they're getting a functional kind of DOTATATE of molecular imaging DOTATATE PET, as well as an anatomic CT scan. And when we say they're getting an FDG PET CT, they're getting a measure of metabolism through the FDG PET scan, and then a measure of anatomy through the CT scan. And patients with neuroendocrine tumors can have many different functional or

molecular imaging studies like DOTATATE and FDG, as well as many different anatomic imaging studies like CT and MR throughout the course of monitoring their disease.

**Lisa Yen**
Thank you for that. I feel like we just got a primer on anatomic and functional imaging. I really appreciate the way that you explained it so clearly. So the second question is, what is the difference between the Gallium-68 DOTATATE and the newer Copper-64 DOTATATE scans? And if there's one that has benefits over the other, what would that be? And should I be getting a Copper-64 scan now that it's out?

**Dr. Gary Ulaner**
Understood. Thanks, Lisa. So if we try and break down these PET agents like DOTATATE, these molecules, I try and picture a key, right? And the key has a part of the key that has all the ridges on it, right? That is what specifies what lock does the key bind to. And then the key on the other end often has like a hole or something that you can attach a key chain or something else on to it. So to design these different PET agents, you have to mix and match. The part of the key that binds into the lock and what you attach on to the key. So, the TATE part of the molecule is that part of the key that binds to the lock. It's a specific structure that binds to the somatostatin receptors on the cancer cells. So anytime you're using TATE, you can bind to the somatostatin receptors and find where the neuroendocrine tumor cells are. DOTA is a linker that allows you to attach the TATE to something that emits radioactivity, right Gallium-68 and Copper-64 are two molecules that emit positrons. So the TATE localizes you to the tumor and then either the Gallium-68 or this Copper-64 emits the positrons and the positrons would allow you to see where the neuroendocrine tumors are in your PET scanner. So the real difference between the Gallium-68 DOTATATE and the Copper-64 DOTATATE is what's the difference between Gallium-68 and Copper-64 because the DOTATATE is the same. The positrons that are emitted from Copper-64 are slightly lower energy than Gallium-68, and that could be an advantage because the lower the energy, the shorter the distance these positrons move. Before we said they kind of annihilate when they hit an electron. So, the lower the energy, the shorter the positrons move, the tighter focus what we call resolution, you can get on the images. So you can get more precise measure of localization of where the tumors are. Really we're talking about the orders of fractions of a millimeter. So, when you say that Copper-64 has this advantage over Gallium-68, through the physics, yes, it's an advantage. Does that translate into a real clinical benefit for patients? No one has ever shown that. So for all intents and purposes, I find the Gallium-68 and the Copper-64 to provide equal quality imaging for patients with neuroendocrine tumors. Now, for hospitals, there's one other difference between Copper-64 and Gallium-68 that is a factor, and that Copper-64 has a longer half life. And that makes it easier for the hospital to order and schedule patients. If there's a delay, the Copper-64 won't have decayed as much as the Gallium-68. But again, in most scenarios, and where we are, what I see at the Hoag Family Cancer Institute, is that we can reliably schedule patients. We're not commonly delayed. So for all intents and purposes, Gallium-68 DOTATATE and Copper-64 DOTATATE provide the same information that you need about neuroendocrine tumors. So do you need to get one or the other? I don't believe so. I believe either are essentially equivalent value for imaging the somatostatin receptors in neuroendocrine tumors.

**Lisa Yen**
Thank you for that. That's really helpful. And just as a follow up with that, if I've already gotten Gallium-68 DOTATATE, should I get another Gallium-68 DOTATATE, or is it better to switch over to Copper-64?

**Dr. Gary Ulaner**
I don't think you need to switch from one to the other. In my experience, it's always better to compare apples to apples when you're doing follow up scans. So if you've had one of them in January, and you're getting your follow up scan in April, get the same scan, because that's going to be the most reliable to compare them together. I don't think either one is essentially better than the other. Once you start using one continue using the same one that provides the easiest comparison among different time points.

**Lisa Yen**
Thank you for that. We always want to have the best comparison with apples to apples, like you said. So the third question is, I've been hearing more about DOTATOC in the USA, where in the past I've only heard it from European specialists. What is DOTATOC? And are there advantages to DOTATOC vs DOTATATE. In addition, what is DOTANOC as well?

**Dr. Gary Ulaner**
Great. So if we go back to our little key analogy, TATE is a key. It has ridges that binds into a lock. And then TOC is a slightly different key. It has slightly different ridges, so it binds a little differently. And the same thing for NOC. These are all three molecules that bind to somatostatin receptors. Now, the most common somatostatin receptors in neuroendocrine tumor tend to be ???. You talk about types two and type five, and there's different extensive binding of TOC, TATE and NOC to these different somatostatin receptors. So for any individual patient, it may turn out that TOC or TATE or NOC is slightly better than the other one. It might give you slightly higher sensitivity for detecting an individual tumor site. Now in the United States, TATE as more specifically Gallium-68 DOTATATE was the first one that was FDA approved. So that was the one that people talked about most in the United States. And now we're seeing that Gallium-68 DOTATOC is FDA approved. So do I think that any one of these is superior to the other others. We're mixing and matching different keys, different portions that bind to the lock and different attachments to the key that omit positrons. Again, for most purposes, these molecules will have nearly equal sensitivity. When you look at a large population of patients in neuroendocrine tumors, for finding sites of disease. In any individual patient, one might work better than another. Although you're not going to know that before you get scanned with all three of the agents. And in general, you're just going to get scanned with one, because all three of them have relatively similar sensitivity. So again, if you're interested in having DOTATOC, you can have that. The most common one we used a somatostatin agent in the United States is DOTATATE. I find that one to be highly sensitive and valuable for the vast majority of patients. And then again, as soon as you start using one imaging method, stick with it, because there can be slight differences between TOC and TATE and NOC. And when you've been treated again, going back to that analogy January to April, if you get two scans of the same agent, then you can make a really apples to apples comparison. Whereas if you use one in January and a different one in April, the question becomes how much has really changed in your tumor versus how much is the change due to you using a different agent. So all the agents are good, and stick with one agent over your course of multiple scans.

**Lisa Yen**
That's really helpful just to have that guideline to try to stick to the same agent with all of the changes out there. And we like to see and hear that there are changes in development, but it can feel overwhelming on the patient. So thank you for that. The next question, we hear a lot about SUV. So what are SUV values? What do SUV values mean on DOTATATE PET scans? And does it translate to a more familiar measurement like millimeters or centimeters?

**Dr. Gary Ulaner**
Or inches right? What is it? 2.54 centimeters to the inch? You gotta get the metric and the old English method. Okay. SUV stands for standardized uptake value. And this is a measure. It's like a ratio of how much of the tracer is in a particular lesion, versus how much of the tracer was administered to the patient. So you can imagine, if the tracer is concentrating in one lesion, the SUV is higher. And if there's relatively less concentration in one lesion than the SUVs are lower. This is not something that you should directly compare to like a size measurement, millimeters or centimeters. And this goes back to that difference between functional and anatomic imaging that we talked about, right? I can look at that tree out my window, right? And all the leaves look the same. I can measure them. This one is 3 centimeters, this one's 2.9 centimeters. This one's 2.8 centimeters. But let's say one leaf is really not alive, it's dead, right? And the other two leaves are functional. They're working. They're undergoing photosynthesis. And I put something in the trees food in the soil, right, that's radioactive. So that is going to undergo photosynthesis. So when I look at those three leaves, I can say this one's 3 centimeters, this one's 2.8 centimeters. But when I measure how much photosynthesis is occurring in each week, one leaf is 0, and one leaf could be 8, right? So that's a real comparison of a size measurement, like centimeters, to a functional measurement like SUV. So in a human patient with a neuroendocrine tumor, if I have a PET CT scan, I could say this liver lesion on the left measures 3 centimeters, and this liver lesion on the right measures 2.8 centimeters. But then when I measure the SUV on the DOTATATE scan, I can say the lesion on the left has no somatostatin receptor in it. The lesion on the right has a lot of active somatostatin receptor in it. Or if I'm doing an FDG PET scan, I could say the lesion on the left is not using any glucose. It's metabolically inert. It's not functional, and the lesion on the right has an SUV of 15, whatever the number turns out to be. That lesion is active, it's alive. It needs to be taken care of. So, SUVs, the higher the SUV value, that means the more tracer is accumulating in the lesion compared to the amount of tracer that you administered into the patient's bloodstream versus centimeters, which is just a measure of size. And again, I like to say that a lesion that's alive versus a lesion that's dead can look exactly the same and have the same size measurements. But they can have drastically different SUV values on these DOTATATE or FDG PET scans.

**Lisa Yen**
Thank you for that. You're taking us back to our high school biology classes with your photosynthesis metaphor there. If I could ask a follow up question about the SUV values. What, if any, ideal SUV values are there? Or would you want there to be? This comes up a lot in our support group and in our webinars as well.

**Dr. Gary Ulaner**
There's no one right answer to that question. It all depends upon what your purpose of doing the scan was. Let's say we're talking about FDG PET scans, right? And before your treatment, your three liver lesions measured 10, 11 and 12. What you want after treatment is for those lesions to measure 1, 2

and 3, right? You want the SUVs to have dropped dramatically after treatment because that means the tumor is not eating glucose, it's not metabolizing. The tumor has been well treated. For a DOTATATE PET scan, you might have an entirely different purpose. The SUV on DOTATATE scans help predict how well you're going to respond to therapies like Lutathera. So when you do a DOTATATE PET before treatment, and the SUV is 2 and a liver lesion, you might say hmm, that liver lesions not taking up my DOTATATE. It's probably not going to take up my Lutathera. So it's probably not going to be treated well by Lutathera. So before these neuroendocrine therapies like Lutathera, you want the SUVs on a DOTATATE PET scan to be as high as possible. Because that tells you that the ridge part of the key fits into the lock of the tumor really well, so that the treatment is going to get to the tumor really well. So bottom line, there is no right answer for what you want the SUV number to be. It depends upon, what is the situation that you're currently in, and what you're evaluating.

**Lisa Yen**
That's helpful. So if I'm understanding this correctly, for an FDG PET scan, you want low or no numbers on that. But for a DOTATATE PET or DOTATOC or any of those other DOTA scans, you want it to be as high as possible.

**Dr. Gary Ulaner**
Well for the DOTATATE and DOTATOC, before treatment with Lutathera, you want the SUVs to be as high as possible because that tells you that your Lutathera is there is going to hit its target really well. And for FDG, it's not as much the number, it's kind of the change, right? So if an SUV of 5 doesn't tell you as much as an SUV of 20, dropping to 5, because if a patient goes from an SUV of 20, before therapy to an SUV of 5 after therapy on an FDG PET scan, that means that therapy worked really well. If the patient went from an SUV of 3 before the therapy to an SUV of 5 after therapy, then that therapy didn't work well. So the the absolute number may be less important than the changes that are occurring before and after therapy.

**Lisa Yen**
That's helpful. So what about after Lutathera? What would you like to see happen with the DOTATATE scans in terms of SUV uptake?

**Dr. Gary Ulaner**
That's a great question. And it's a really complicated question, unfortunately. Because the DOTATATE scan sees the somatostatin receptor. So you can either really, after therapy, let's say that the SUV and a DOTATATE scan was 20 on a lesion before therapy. And then after the therapy, the SUV is 5. Well, there are two potential interpretations of that. Number one is that the therapy worked and there's less tumor, right? That makes sense. But the other potential interpretation is the tumor still there, but it's losing its somatostatin receptor, and when it loses somatostatin receptors it tends to get more aggressive. So that could be bad. So whereas with FDG, the change in FDG, before and after therapy really gives you a really reliable measure of, is the tumor getting well treated or not well treated? Changes in somatostatin receptor agents like DOTATATE before and after treatment are not as reliable because you don't know which of those two processes are dominating. That's why with the DOTATATE scan that tends to be done prior to Lutathera in order to make sure that Lutathera is going to be effective, right? If your SUVs are really low on the DOTATATE scan then they're not going to prescribe Lutathera. Why should you get a treatment with side effects, if it's not going to hit the target and give you benefit. But there's less work done on measuring treatment response, right? Before and after

treatment with DOTATATE, I find that FDG has been the most reliable of the radiotracers for measuring treatment response before and after treatment.

**Lisa Yen**
Thank you. That's really helpful. This is an area that there's a lot of confusion, so hopefully that helps clear up some of the confusion. And you've really given us very good and clear explanations here. So if we could move on to anatomic imaging scans, and you've already explained a little bit of the general category, the next question is what is the difference between the CT scan and a DOTATATE PET CT scan, and "regular" CT scan that might be ordered?

**Dr. Gary Ulaner**
You got it. So let's talk about a CT scan without the DOTATATE PET or that quote unquote, "regular" scan. That scan, which some people call a diagnostic quality CT scan, There's no one uniform term yet. I wish there was one. But there's no one term that best describes it. But essentially, the standard CT scan that's done on its own, is done with ample amount of penetrating radiation to give you very exquisitely detailed images of bone soft tissues long and where the lesions are in those images. So you optimize the amount of radiation that's used in order to get really good images. That's number one. Number two is those scans are often done with what's called intravenous contrast. And that contrast goes into your bloodstream so that you can see the vessels really well. And then tumors often have increased blood flow. So the contrast helps you see tumors, right? And then third, that CT scan is usually done with the patient holding their breath. You take a deep breath, you hold it and the scans done while you're holding your breath. And that's the best way to get pictures of your lungs. Because when your breath is held, you can get really excellent resolution of small lung nodules that could be metastases. Now, when you do a DOTATATE PET CT scan, you may use some of those three things, or you may use none of that. So let's talk about the standard DOTATATE PET CT. Number one, we use lower dose radiation on the CT, so we don't get such exquisitely detailed pictures. And we do that because the CT component of that PET CT is being used for a few things. Namely to optimize the FDG PET or the DOTATATE PET. So you're trying to see the lesions with the FDG or the DOTATATE, not necessarily with the CT scans, we use a lower dose of radiation. Second, it may not be done with intravenous contrast. So it's a non-contrast CT. And again, the contrast sometimes helps you see lesions, but you're using the DOTATATE or the FDG to see the lesions not the intravenous contrast. And finally, PET CT scan, on a typical scanner these days, takes 8, 12, to 15 minutes, you can't hold your breath that long. So PET CT scans are done with free breathing, not with a breath hold, and that makes it harder to see small little nodules in the lung. So a standalone PET CT is done optimally to see lesions. The DOTATATE PET CT make some sacrifices in the quality of the CT in order to optimize the PET side of the equation. Sometimes you can get a PET CT scan that tries to optimize both sides, right? And you can never get 100%. You can use full radiation dose on the CT scan and you can use intravenous contrast on the CT scan. But you can't do breath hold on a PET CT scan, unless there are these really modern scanners that only one or two places have that can take pictures in a matter of seconds instead of a matter of minutes. So you can hold your breath that long, or you're one of these surface divers that dives for pearls and you're able to hold your breath for 12 minutes. So generally, you can't get the best of both worlds all the time. But I like to do my PET CTs with as close to optimal CT performance as possible. And that includes using the full radiation dose, and using intravenous contrast, so that you get the best quality CT that you can get, as well as the best quality FDG or DOTATATE PET that you can get.

**Lisa Yen**
That's really helpful. We definitely don't want people passing out in the CT scanner. And so definitely trying to optimize the scan for whatever the purpose is. This next question ties into what you're already touching on. What type of CT scan should be done to evaluate NET, and should a CT scan be done with contrast, and if so, what type of contrast?

**Dr. Gary Ulaner**
So for a CT scan, the contrasts are iodine based. And again, this is to help visualize differences in tissues as best you can. I like CTs done with intravenous contrast. It's not always performed that way, nor is it always needed that way. For example, if you have a patient with lymph node, liver, and lung metastases that are really DOTATATE avid on that scan in January, and you want to see treatment response in April, then a DOTATATE PET CT that doesn't optimize the CT is probably more than enough, right? Because if the DOTATATE PET is giving you the majority of your information, then you just optimize the DOTATATE PET side. For patients who are initially diagnosed with neuroendocrine tumors, I like to make sure that patients get a intravenous contrast enhanced scan as part of their initial workup. Because you can sometimes see lesions on the CT, that for whatever reason, you don't see on the PET. Whether they express somatostatin receptors really poorly, so they don't show up on the DOTATATE PET, or whether they're not very metabolically active, so they don't show up on the FDG PET. Sometimes you can see lesions on a contrast enhanced CT or an MR that don't show up on the PET scan, and therefore an initial diagnosis of a neuroendocrine tumor, patients should have, I think, at least one functional imaging scan and one well performed anatomic imaging scan, and then again, like PET CT, those can be performed at the same time, if you're doing your DOTATATE PET CT with full radiation dose and intravenous contrast. So do you need to have IV contrast? Depends upon the individual situation. At initial diagnosis, I highly recommend you get at least one anatomic imaging with intravenous contrast. Follow up scans, it depends whether your tumor was better seen on the PET or on the CT. If you have a tumor that wasn't seen on the PET, then obviously you want to optimize your CT. If you have a tumor that was best seen on the PET, then you probably want to optimize the PET. You don't necessarily have to optimize the CT component on your follow up post-treatment scans.

**Lisa Yen**
Thank you. That's really helpful. I know that comes up a lot about whether or not you should have contrast. Thank you for explaining that. And a follow up question to that, people have heard this term triple phase CT scan. What is that? And how do we know if we are having this type of scan?

**Dr. Gary Ulaner**
Got it. So the phase refers to the point in time after you administer intravenous contrast. So for a standard CT scan with contrast, they will give the IV contrast and then they take the pictures, maybe 30-40 seconds later when the contrast has had enough time to get into you. Let me back up a second there and say they put the IV contrast into a vein in your arm, right? Let's think about what happens to that contrast. The contrast is in your vein, it travels back to your heart so it's in your venous system, and then your heart pumps it out into your arterial system, right? And the arterial system goes out to all your organs, into the capillaries, and then from the capillaries it gets sent back into your venous system again, right? Blood is constantly going veins to arteries, from your heart to the arteries, through your capillaries back into the veins and then back into your heart. So depending upon how long you wait after you administer the intravenous contrast, you will see different things. You will see different

places that this contrast is in your bloodstream. So when someone does a triple phase CT, typically that means they're scanning in the arterial phase first, when the contrast is in the arteries. And then in the venous phase, a little later, maybe 30-40 seconds later, when the contrast has moved through the capillaries and back into your veins, and then finally, in a delayed phase, which could be minutes after that, and the contrast is now being excreted into your kidneys. Alternatively, triple phase could mean the first phase is before I give the contrast at all. So it's a non contrast CT. And then the second phase is that arterial phase and the third phase is the venous phase. And then some people will talk about four phase CT, right? And that's all of it. Before you give the contrast, one. Arterial phase two.Venous phase, three, and delayed phase, four. And depending again upon what is the individual application of that scan, you might do one, two, three or four different phase. Neuroendocrine tumors are kind of special, in that they are often visualized best on the arterial phase. So while most cancers are best visualized on the venous phase, neuroendocrine tumors are often but not always best visualized on the arterial phase. So for patients with neuroendocrine tumors, patients often get scanned at multiple points in time. That's the triple phase or quadruple phase, in order to see what each different point in time can show. You get at least at arterial phase, when the cancers are often best seen, and a venous phase when other things of importance can be best seen, like other benign lesions that need to be excluded from being cancer. And then you might do a phase before the contrast is administered that helps you document where calcifications are in the body because after you give the contrast, the calcifications can be confused with contrast. And if you have a pre contrast phase, then I can say, ah, this really bright white stuff, that is not my contrast because I haven't given the contrast yet. That must be something calcified, or something else. And then the delayed phase, the fourth phase, is most common for visualizing lesions that are in the genital urinary tract, like the kidneys, the ureter, and the bladder. So when they say triple phase CT, that means they're giving you a bolus of contrast, and they're putting you through the CT scanner multiple times at different time points in order to see where the contrast is at those different time points.

**Lisa Yen**
Wow, that's really helpful. And how would the patient's know if they're having this type of scan?

**Dr. Gary Ulaner**
You move through the scanner more than once. So when you're sitting on the scanner, they often will put you through quickly once and that is what they call their scout. They line up where they need to visualize. Say they're going to scan your chest, your abdomen, your pelvis, they get their landmarks of where you're going to go through the scan. It's the quickest part of the pass through the machine. In a second or two, you've done your scout. Then if you go through the machine one more time, you've only had data captured at one phase. If you go through the machine two more times then they captured two sets of data. And if they go through the scan three times, then that's your triple phase CT. Patients know when you get intravenous contrast. If you've ever had intravenous contrast, you can feel it going into your arm, you tend to get this flushed, warm feeling all over your body. So if they send you through the scan before they do the IV contrast once and then they send you through the scanner twice after they give you the IV contrast, well there's your 3-phase or triple phase CT.

**Lisa Yen**
That's really helpful. So if you've lived through it, you know and you can count the number of times you've been through it.

**Dr. Gary Ulaner**
Yeah, how many times they send you to the scanner?

**Lisa Yen**
Yeah, well what if you're not the person and you're a loved one? Would you be able to see on the report or on the order?

**Dr. Gary Ulaner**
Under the method section, most reports have a very similar structure. They start with saying what the scan is at the very top. This is a CT of the abdomen and pelvis. Or they say this is a DOTATATE PET CT. Sometimes they'll even say in the header, this is a three phase CT of the abdomen or pelvis. But certainly just under that there'll be a method section where they explain what they did. And they'll say in there for three phase CT, the patient was scanned through the chest, abdomen and pelvis before IV contrast in the arterial phase and in the venous phase. And that's your three phases.

**Lisa Yen**
Absolutely helpful. Thank you for that. So now we know where to look on the reports as well. So we've talked about PET scans, we've talked a lot about CT scans, and now moving on to MRIs. What is the difference between CT and MRI, and what type of MRI scans should be done to evaluate NET?

**Dr. Gary Ulaner**
Excellent. So CT scan measures density. Actually, it measures something called attenuation, which is the amount of radiation that is absorbed as the radiation passes through your body. But I think it can be simplified by thinking of it as density. Bones are denser than soft tissue. Soft tissue is denser than air or gas, right? So you can see bones from liver and from long through the different densities on a CT scan. And that's how the CT scan works based on density. MR is based on magnetic moments. If you've ever been in an MRI scanner, it's really loud. You hear this, *mimicks noises*. Now what that is, is the magnet. What they do is your body is in itself, a really weak magnet. Your water molecules have a slight magnetic moment, and each water molecule is facing in a different direction. So in total, your magnetic moment is zero. But each individual water molecule has a little magnetic moment. So the MR scanner using a really powerful magnet lines up all those water molecules in one orientation. And then you are essentially a little magnet. Right? And when the magnet stops working, those water molecules, they go from being all orderly, to going back to being disordered over time. And as they're flipping back to being disorderly, you lose your magnetic pulse. And the MR can distinguish tissues based on how long it takes these magnetic poles to dissipate. So an MR sees thing things differently than a CT scanner, right? The CT scanner is seeing things through density, the MR is seeing things to these magnetic poles. And it's complicated, but I think it can be incompletely sub optimally but a nice summary would be that the CT is better than the MR in seeing the bones and the lung. Whereas the MR is better than the CT at discriminating different soft tissues. So the MR can see liver nodules in the liver with a greater sensitivity than the CT scan. CT can. So if you imagine, if your normal liver has a density that we call 100, right? And then a nodule appears, right? This is a metastasis. You want to detect this. But the density of the nodule is only 99 or or 98. We may not be able to discriminate those small differences on the CT scan until the nodule gets much bigger. And then we can say, ah, now my eye or a computer algorithm can discriminate that yes, there's a nodule here that's different from the rest of the liver. The MR scan is much more sensitive for finding things in structures like the liver. So if there is concern, for example, we do a CT scan or a PET scan or a PET CT scan, and we say, hmm,

there might be a lesion here in the liver, but I'm not sure. The next step is to get an MR because the MR will be able to tell us more definitively, yep, something's there, or no, that was just some some background noise. So MR and CT are both anatomic imaging methods. They image using different physical methods. And they each have strengths and weaknesses, where the CT tends to be better for the bone and the lungs, and the MR tends to be better for the soft tissues in the CT scan. And that makes the MR the preferred modality and the preferred anatomic imaging modality for things like the liver and the brain.

**Lisa Yen**
That's really helpful. You have a remarkable way of breaking things down in a way that is easy to understand. So we've talked a lot about contrast with the CT scan, what about with an MRI? Should an MRI be done with contrast, and if so, what kind of contrast?

**Dr. Gary Ulaner**
It all comes down to the application. For most cancer applications, MRs should be done with intravenous contrast. The contrasts are different than the contrasts that they give for CT. Again, for CT, it tends to be based on iodine. For MR, they use agents that help optimize these magnetic signals that we can get from the MR. Terms for MR contrasts are, Gadovist®, Magnevist®, Eovist®. And for CT scans essentially all these IV contrasts are the same. For MR, there is an important difference between Eovist® and the other types of MR contrasts. Eovist® has the advantage of being excreted through the liver. So a normal liver takes up the Eovist® really well. So that's something that can be used to help visualize things that are not supposed to be in the liver, like metastases. On delayed phase images, right, we talked about these phases, arterial phase, venous phase, delayed phases. On a more delayed phase image, the liver should have some Eovist® in it, where as a metastasis in general does not. So Eovist® helps visualize liver metastases to an extent that's a little greater than other MR contrast medium. So then, again, should you be getting intravenous contrast for an MR scan? Depends on the application. For most oncologic applications, if you're trying to see a tumor, yes, you should have IV contrast for an MR scan. And then which MR contrast agent should you be getting? Just know that Eovist® provides a more sensitive evaluation for liver metastases than the other MR intravenous contrast agents.

**Lisa Yen**
Okay, so it sounds like Eovist® is the contrast of choice for the liver. That's what you're saying?

**Dr. Gary Ulaner**
I believe so. Yes. That is my that is my opinion. And I think that is a predominant opinion among people who when they're choosing contrast agents, if you have liver metastases, medium is the little superior to other IV contrast agents for MR.

**Lisa Yen**
Okay. Thank you for that. And again, now we've talked about CTs and MRIs and PET scans. How concerned should patients be with radiation safety? Given that they're getting all these scans, CT, MRI, DOTATATE, and then also PRRT. You and I know that there are patients who tally the amount of radiation they get over a lifetime. So, how concerned should they be?

**Dr. Gary Ulaner**
Great question, and a question that we are often responding to. Now I approach this from two different points of view. Number one is the principle in medical imaging called ALARA, which is as low as reasonably achievable, which means we try and keep radiation to an absolute minimum. Now, the reason we do that is because there's evidence from people who have had lots of radiation, atomic bomb survivors, that these patients have higher cancer risks in the future. Right? So if you've been exposed to a really high level of radiation, you are at increased risk for developing a cancer in the future. So there is a push to decrease the amount of radiation given during medical imaging. And that is the point of view I take in patients who have kidney stones. I've seen a number of patients that have lots, they have repeated kidney stones, they have repeated flank pain, they have repeated treatments for these stones that have struck the ureter. And if a patient is going to have 40 CT scans during their life and they only have kidney stones. They don't have cancer already. You probably want to try and lower the radiation dose as much as you can while still getting the information you need from the images to optimally treat the patient. So those are patients that don't have a cancer, they have benign things that they're getting imaging for, and they might get repeated imaging for, we try and lower the dose. For patients that already have cancer. the information that you get from these diagnostic imaging studies, like CT or PET scans, the amount of radiation is actually quite low. And the information you get from the scan is really valuable. So I say, optimize the value of the scan, because you're going to get a scan that's going to try and determine what treatments you're going to get, or whether you're going to change treatments for your cancer, you better do the study right. And there may be a hypothetical risk of some cancer way in the future. But the information you get today, if you treat your cancer correctly, it's going to far outweigh any hypothetical risk of developing another cancer some point in the future. And I say hypothetical, because we know with high doses of radiation, like we said, atomic bomb survivors, there's definitely an increased risk of getting cancer in the future. What we don't know is that low levels of radiation, do you have any? Do you have a small increased risk? People think, well, if you get a million units of radiation, you get this million units of increased risk? Well, what if I only got three units of radiation? Do I have three units of increased risk? And if you draw a straight line, you presume this linear relationship between radiation and risk, then that's what you would presume. But there's actually no evidence that that is the case. And we've never been able to show that patients getting diagnostic imaging are at higher risk of actually having cancer in the future. We use that ALARA principle to say, since we don't know we're going to, whenever we can, keep the radiation dose as low as possible. So for me patients who have cancer, get your CT scans, get your PET scans as you need them in order to maximally guide your care because the benefit you get from the scans will far outweigh the hypothetical risk of getting some future malignancy that we don't even know if it's true that there really is a risk at low radiation levels. MR scanners don't have any ionizing radiation. There are different risks from MR. MR can cause thermal injuries from, again, these magnetic poles that are produced in your body are not entirely benign. But when you're talking about radiation, MRs have no radiation, CTs and PET scans and X rays, things like that, have small amount of radiation. And then we get to things like PRRT. Right? This is the radiation therapies. Also like external beam radiation. Things that we're trying to treat cancer with radiation. Now, this is not no longer in the range of small amounts of radiation. These are huge amounts of radiation. I like to make the comparison of these radiation therapies like PRRT, or external beam radiotherapy, that's like getting an Olympic sized pool amount of radiation. And a CT scan or a PET scan is like adding a drop of water to the Olympic sized pool. So if you've ever had PRRT, or you've ever had external beam radiotherapy, to me, it doesn't make much sense to worry about the radiation that you're getting from a CT scan or a PET scan. It's one 1,000,000th of a factor of what you've already been exposed to. So if people routinely get PRRT or external beam radiotherapy to

treat their cancers, then getting CT scans and PET scans, the amount of radiation is essentially very near zero. But be aware with PRRT and external beam radiation because now you're getting a very, very high dose of radiation. Those treatments do come with the potential risk of causing another cancer in the future. PRRTs are known to have about a 1% risk for a hematologic malignancy, a malignancy of blood in the future. And external beam radiation has been associated with malignancies particularly with sarcomas that occur in the bone or the soft tissue. So should you be wary of the radiation? Through the principal of ALARA? Yes. So don't get radiated unless the benefit of the radiation exceeds the risk of the radiation. If you have kidney stones, don't get a CT scan every time you have flank pain. You don't want 40 CTs for kidney stones. You don't want the hypothetical risk of developing a cancer just from treating kidney stones. If you have a cancer--a neuroendocrine tumor, breast cancer, lung cancer, get the imaging you need to optimally manage your tumor that far outweighs any hypothetical risks from the radiation. And then if you need radiation therapy, you get the radiation therapy because the benefit of the radiation to kill your current tumor is so much higher than the risk that you have from developing another future tumor. So bottom line, don't get any radiation that you don't need. But if you need it, get it because both diagnostic levels of radiation and therapeutic levels of radiation have been proven to be extremely helpful in patients and managing cancers.

**Lisa Yen**
Thank you for that. That's a very clear explanation. I really liked that summary. Get the imaging and treatment that you need and when you need it. So thank you for that really clear explanation of the radiation safety and how to weigh the risks and benefits around it. So shifting gears a little bit. What do you suggest for those whose tumors don't show up on scans? What scans might you do for someone that doesn't have uptake? On that Gallium-68 DOTATATE PET CT scan? And what about those whose tumors don't show up on any scans at all.

**Dr. Gary Ulaner**
So there's the statement, to each their own. And in individual patients, one type of scan is going to be better than another. For neuroendocrine tumors, the functional imagings tend to be better than anatomic imagings in many cases, but not all. So if you are looking to do Lutathera, then you want to get that Gallium DOTATATE, or a similar PET scan. Because if the tumor does not take up the Gallium DOTATATE, or the Gallium DOTATOC or the Copper DOTATATE, whichever one that you're using, it's not going to take up the Lutathera. Right? The negative DOTATATE is really valuable, because it's telling you to use a different type of therapy other than therapy targeted at this somatostatin receptors. FDG is really valuable in most patients for tracking treatment response. So if your tumor at baseline is FDG avid, you get a therapy then you use a follow up FDG to show that the FDG avidity has gone down, and that is more reliable than anatomic imaging with CT or MR. But what if you have a tumor that doesn't show up on DOTATATE, or doesn't show up on FDG? Then you move to your anatomic imaging. There are low grade neuroendocrine tumors that you may not see well on an FDG PET, and then you need to measure size on CT or MR in order to better term with the tumors getting bigger or smaller with therapies. And what happens if you don't show up on any of those scans? Well, in general, if you don't show up on any scan, molecular, functional or anatomic, your volume of disease is probably pretty low. So that's a good sign in and of itself. Because when things get big enough, they can usually be seen on virtually anything. So if you're so small, the tumors are so small that you can't be seen on anything, take that as a blessing and hope it stays that way as long as possible. But imaging is not the only way we track neuroendocrine tumors. We know that there are blood tests, molecular markers that are used in addition, and of course, this is often how neuroendocrine tumors

are initially diagnosed. Do you have a symptom from a functional neuroendocrine tumor? And then you run a blood test, which shows something being secreted into the blood that says, there's there's something here that's not supposed to be here or is here in too high of an amount that suggests a neuroendocrine tumor, and then you get the imaging to see where it is and how much of it is there. So if you can't be found on imaging, there are still other laboratory tests that can be used to track the extent of disease. For a patient that has a non functional tumor that doesn't show up on any scans, again, I say count your blessings and hope it stays that way for as long as possible.

**Lisa Yen**
Thank you for that. We've really covered a lot of the scans here. So the last question really has to do with reports. As you know now on the day have electronic medical records, people can get their scan reports. So what suggestions do you have for patients who are trying to understand their scan reports. And too many of us, it's like Greek. So any advice would be greatly appreciated.

**Dr. Gary Ulaner**
I think I've done a different session on interpreting scan report. And I don't think we have the time to go into all of it. But know that reports are usually structured with different sections. That initial header telling you what the scan is, and what was the methodology under which scan was performed. A finding section that tells you what is seen. And then an impression section, which is what the radiologist is trying to convey, what is the importance of those findings? So try not to get lost in the details of the finding section. There's often a lot of confusing words in there often that have no clinical implication...hemangiomas and things that are properly buried in the finding section. Go to that impression. That impression is kind of like your cliff notes for your report. And there are different strategies people employ for doing impressions. I think the two that are most valuable can be the TNM, tumor nodes metastases. Some people organize their report, they tell you, do I see a tumor? Is the tumor getting bigger or smaller? Do I see nodes? Are the nodes getting bigger or smaller? Do I see distant metastases? Are they getting bigger or smaller? And then of course the distant metastases tend to be the most important element there. So if primary is getting smaller, the nodes are getting smaller, but uh oh, there are new liver metastases, take that as not a positive course. The other way that reports can be organized is that final statement, is there more disease, less disease, stable disease? For some tumors, stable disease is not a great thing. But for neuroendocrine tumor, as I like to say stable disease is a wonderful thing. Neuroendocrine tumors, if you can keep them from growing, patients tend to do well. So if you're getting Lutathera treatments, and six months later you go get a PET scan or a CT scan, and they say stable disease, don't think that the therapy didn't work. The therapy did its job, because without the therapy the tumors could have been bigger. So a lot of patients who have therapies for neuroendocrine tumors, the tumors never shrink. But as long as they're not growing, that's a wonderful thing until we develop better technology to better treat the tumors that we face today. So on these reports, read the first sentence, so you know what type of scan we're talking about, and then go to the impression and look for that. Is it worse? Is it better? Is it stable? And better or stable are wonderful things for neuroendocrine tumors. As a final little tip, try and figure out when they say, hey, it's better or it's worse, or it's stable, make sure you know what they're comparing it to. Because, particularly, if you get your scans in different locations, you go to hospital A, you get one scan, you would a hospital B, you get another scan, you got to hospital C, you get a third scan, imagine that, I'm going to oversimplify this, but on your pretreatment scan at hospital A, they found 10 lesions. And then on your post treatment scan at hospital B, they found three lesions, but they didn't have scan A to compare to. So they say, oh, we just see three lesions, but they can't say it's gotten better, because they don't know it's gotten better. They don't have the comparison. Then

you get another scan at hospital A again, and there are five lesions. Hospital A only has the first and the third scan. And they go, it's better. But it's actually worse compared to the second scan. So know what they're comparing it to. Because if there are missing scans, there's missing information. And that also means when you go to a different hospital to have another scan, try and be vigilant in making sure they have as much prior information, particularly the most recent scan, available for their interpretation, because if they don't have those appropriate comparisons they can end up making the wrong conclusions.

**Lisa Yen**
Wow, thank you so much for all of this. Your time and generosity and the way that you explain things in such clear and simple terms. You really demystified a topic of scans and understanding scan reports. That's very challenging for many people. So we really appreciate your time. I've really enjoyed this. I could listen to you talk about this for hours, but I think we have to have an end to this podcast. We really appreciate all your work in this field, your time with us and your dedication to the neuroendocrine tumor patients that you see.

**Dr. Gary Ulaner**
Lisa, it's been my great pleasure to be here. Thank you for bringing attention to this important topic. And I wish my best to anyone who's listening here through their medical care and medical care of their loved ones.

**Lisa Yen**
Thank you again. Thanks for listening to The LACNETS Podcast. We want to thank our presenting sponsors Ipsen Pharmaceutical and Advanced Accelerator Applications. For more information about neuroendocrine cancer, go to www.LACNETS.org.