THE LACNETS PODCAST

With Sue Chang, 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. Thank you for joining us for today's episode of The LACNETS Podcast. I'm excited to introduce today's guest, Dr. Sue Chang. Dr. Chang is an Assistant Clinical Professor and Chief of the Division of Anatomic Pathology in the Department of Pathology at City of Hope here in Duarte, California. She graduated from Harvard University and went on to receive her medical doctorate from the New York Medical College, and she later completed her pathology residency at UCLA health. She furthered her training at UCLA health, and as a surgical pathology fellowship at Brigham and Women's Hospital in Boston. She has been published in many peer reviewed literature, and has presented her work nationally. And all that is to say that she really knows her stuff, especially in regards to NET. Dr. Chang has joined us for in person meetings when we used to do those at City of Hope and also for our first COVID webinar back in 2020 when the pandemic first hit. For more information about pathology, and for videos and slides, you can go on our YouTube channel. So Dr. Chang, we're really excited to have you, and before we get into the 10 questions for today, could you tell us, what is pathology? And what made you interested in pathology?

Dr. Sue Chang
Sure. Thanks for having me on the show. Lisa, it's really nice to chat with you again. I forgot that we were the first webinar during COVID. I remember the scramble to figure out the AV stuff. Now you and I are like AV experts. Not really. Remember when I was like, how do I log on to zoom? And now I'm like running three zooms at one time. It's pretty remarkable. So it's really nice to see you and chat with you again. You mentioned that I went to medical school in New York, and I ended up doing residency at UCLA, what I didn't mention, and it doesn't fit in a little webpage bio, is that for a long time, I thought I was going to become a surgeon, for a really long time because I like spatial reasoning, surgery certainly is interesting, it's extremely gratifying in that you get to meet your patient, you get to do a thing that really individually helps the person. But when I was in med school, I kept disappearing to go to the frozen section room of the pathology lab. I would follow the specimen and I would follow it to the answers. And so it was always really gratifying, not just to have seen how it happened, but also to get the answer. What is this tumor? Is it involving certain organ systems? Is there a lymph node

involvement? So, after a while, it takes a long time to know yourself, and at the time, I was like, early 20s, but after a while, I was like very slowly, oh, maybe it's pathology. And I think sometimes what happens is you don't see a lot of pathologist in TV shows. Or every once in a while on Grey's Anatomy, I think they show a pathologist but it's almost universally unflattering, or strange. And it's not as "name in lights" type of thing. So it's fairly behind the scenes. It's extremely gratifying, but in a different way. So one of the ways I like to explain the pace and nuance of pathology is like football versus golf. So football, they make tons of movies about it, tons of TV shows. It's very splashy. And to me, that's a little bit like surgery. Everyone knows, they can name someone who's a surgeon or their best friend's parent was a surgeon or something like that, and they make TV shows about it. And pathology is like golf. When you're watching golf, it's so boring because you're watching them and they're like squinting in the distance and thinking really hard. And you're like, this is so boring to me. But then, when people play golf, they're like, this is the most interesting sport. This is the most mentally challenging and satisfying thing. And so if you're in it, you get it. And if you're not in it, you don't get it at all. And I think that's how I think about pathology, and not everyone can name golfers. There's a couple of golfers out there but most people don't. And that is how I feel about the PR issue of pathology, but it is very cerebral. It's immensely satisfying. It's very intellectually stimulating. And you don't really hear about it too much. So I am on a one person mission, there's a few of us actually, to let people know how important it is. There's an often cited statistic from a few years ago that something like 75% of medical decision making is actually performed based on data from laboratory testing and pathology reports.

Lisa Yen
Oh, true. Wow. Especially in NET!

Dr. Sue Chang
Yes, especially in NET. The classification and the terminology that's used really drives clinical management. It drives prognosis. It drives the conversations that you and your doctor have. And so I take that responsibility really seriously. And all the pathologist I know, take that responsibility really seriously. We're the most conscientious people that I know. And that's among doctors, which is a pretty conscientious group as a whole.

Lisa Yen
Wow! We're really grateful for that, because as we just mentioned, it really does drive many of the treatment decision making for NET. So, most patients, their only awareness of pathology and the field of pathology might be that they get a pathology report. And you even take it a step further, they know that they get reports in general. So people get lab reports, they get radiology reports, and they get pathology reports. And it's all a mystery, because all in that field of reports where they don't see a person. So what is pathology? And how do they distinguish it from radiology and other reports?

Dr. Sue Chang
So there are two ways you actually interact with the pathology department. The first I think it's the most. I can't think of a single person who hasn't had a lab test. Your complete blood count, your fasting glucose, your hemoglobin A1C. Even if you do a urinalysis, a lot of those usually are done by the laboratory. And so those reports come out, they look like a very line item test result report. And those tend to be more common, easy to understand. They give you a range even. Sometimes if you're out of the range, put a little asterisk or it turns red. And so that whole thing is, by the way, a lot of development about trying to make things as readable as possible because it certainly doesn't come out of the machine that way, right? It doesn't come out with a nice little bar graph with a little asterisks if you're out

of range or a little red exclamation point. But that is all long term work between laboratorians and scientists and patient people who are trying to make these lab tests more readable and understandable. The pathology report is also coming from the same sort of section of the hospital but looks very different. There's a lot of words. The number one thing I always say is when you get your report, look in the top upper right hand or upper left hand corner and make sure it's your name. You would be surprised how many people read the middle and the final diagnosis, and start to spiral. And then you go, oh, it's not my report. It's a little less common now that we all have electronic medical records, and you have your access on your phone where you have to log in. But in the past, if you're all printing everything on the same office printer, if your clinic has the same one office printer, someone might pick up the wrong report, not double check, and hand it to you. So that's number one, we always do that. I mean, I do that all the time. With my slides, I always am looking at the name making sure it's the right one before I send it out. This is an easy way to make sure that no one unnecessarily goes through sort of an emotional trauma. And then the next thing is that you might notice that usually there's a section called final diagnosis or diagnosis. And that is the marquee top line, most important thing I want everyone to see. And when I'm writing a report, I am writing it for three groups or three audiences. The first always is for the patient. So it's on me to try to explain in as clear and as few or as many words as needed, what the final diagnosis is. And I would say 75-80% of the time, it's clear cut. So there's few words, I know exactly what's going on and we write it down exactly the way certain governing agencies like the World Health Organization, or the FDA. There are certain things that we have to say in order to count as belonging to this diagnosis. I'd say 80% of the time it's fairly cut and dry. And then I might give you some details that I think are important. More likely than not, if I put in some details in the top marquee, it's also for your oncologist, your surgeon, the radiologists in some respects, to know, hey, I saw this I called it this, I categorize it such way. Here are some pertinent details that you will find important, whether it means that it changes your thought about chemo, or it changes your thought about follow up, or it motivates you in a certain way to do a certain type of surgery or not do a certain type of surgery, here's information I think would be important for you, my colleagues in surgery in oncology, in radiation oncology, here are things I think you will want to know. And the third audience is for other pathologists. Very frequently the way that large institutions such as City of Hope work, we have a huge coterie of pathologists. So just because I see your biopsy doesn't mean I necessarily get to see your resection. Or if you come back in four or five years with a repeat biopsy, I may or may not be the person who receives that biopsy. So when I write this, I'm writing for the future pathologist, the next pathologist. Or if you're going to go get a second opinion somewhere else, and that pathologist at that institution talks to that surgeon, I want them to know what I saw so that they can confirm. I think of it as like a handoff like a baton in a relay race. So here's all the stuff that I think you need to know. And then you can go ahead and continue the race. So in terms of when I write a report, I'm thinking about three different audiences, which might be why sometimes these reports seem so esoteric. I know there are words in there that patients don't understand, and there are times when I would say I wouldn't stress too much about like the second or third or fourth page, because a lot of those times those words are details and they are not the marquee things I need you to read. Everything I need you to read is under the final diagnosis. And there might be a comment if I decide to get literary and want to write something or call attention to something. But those are the top two. I really understand it because I've been a patient myself. When I get a report, my brain shuts off. I'm so panicked sometimes. I've seen my parents looking at like a biopsy and you can't see the words because you're spiraling already too far in your own head. I get it. So if that's what happens and all you can do is get through the first page, that's fine. That's all you really need. All those other pages, you can shove it at your surgeon, at your oncologist and be like, have you read all of this? And they probably have because I get phone calls from my colleagues and they're like, on page seven you said... what

does that mean? And I always barely gratify that someone is reading for detail because that's why I put it all down there.

Lisa Yen
That's amazing. It's so reassuring to know that you're communicating with three different audiences not all for the patient. You're giving permission to not have to understand every little detail of it.

Dr. Sue Chang
You don't have to. If you hand it to your someone who's helping you through this, and they're able to come through it, just highlight some questions. You don't have to read it, somebody has to read it. It can be really esoteric. And just know you're not gonna get quizzed on it. I'm not going to ask you like reading comprehension. So really it's for you to have in your hand to take around and make sure other people get the baton and get it correctly. That's the power of the report. One of the other things about most cancer centers is that people who work in NET, people who work in this group tend to talk to each other all the time. So our surgeons or oncologists, we meet maybe every week. I get phone calls all the time. We're all constantly in communication. But that communication is in the form of emails, it's in the form of secure messages, but it doesn't go with you if you're going to go to another institution. So it's really important to me that that document that you have, which is the pathology report, that captures everything I might tell your surgeon over at USC. If I had the chance to talk to your surgeon over at MD Anderson what I would say. And we don't always get to do that so what I haven't said is this paper, enduring material that you can bring to them and they can see and go, oh, I know what she's trying to tell me. Even though I've never met your surgeon over there. I've never met your oncologist that you're going to see somewhere else.

Lisa Yen
Yes, and that baton becomes a really important piece. And so from the patient's standpoint for a NET pathology report, what should I, as a patient or caregiver, pay attention to in the report? I know you mentioned the final diagnosis, but what are the important pieces?

Dr. Sue Chang
The first thing I would see is if you had a biopsy or a surgery, we always write the location. So if maybe you had a core biopsy of your liver, it should say something like liver, biopsy. Core biopsy of liver or something like that. Make sure that the place that you were told you were getting biopsied is the thing that I got to look at. If you have had an appendix resection, make sure that it says appendix and then any other parts that maybe was part of your surgery. The second thing I would want you to read is that final diagnosis, marquee diagnosis. Basically what pathology does, this is very general, is we group like with like. Some days, I feel like it's all my job is, putting things together and corralling all them and saying, okay, you guys are a team. You guys are one group, because you all kind of look the same, you all kind of do the same thing, you all kind of behave the same way, and so we're going to group you all together and run a bunch of data on you to try to understand what happens when people of this type of grouping have this type of tumor. So I would look for that. And the World Health Organization publishes essentially, categories. Sometimes I think of them like menu options, and so you try your best to understand which one it should be in. Sometimes they don't. People always being people defy categorization. And those are the times when you like really have to put on your thinking cap and problem solve and either do a best fit, or make a suggestion, but sort of keep the dialogue open. So the thing that you probably would find the most useful, especially for carrying that baton is what category is this in. And you will see words, especially in the NET field, you'll see words like well differentiated and

poorly differentiated. You'll see grade one, grade two, grade three, you will see large cells, small cells. So those are the words that you will commonly see. And what will happen is that the combination of those words puts this tumor in a particular category. And that's really important for prognosis, because every person is different. But we try to make generalizations so that we can give some sort of signaling and try to understand what particular tumors do. And then the other thing is that treatment is also dependent on the way we categorize things. So I don't mean to make it sound like pathologists are like the most important people. But I do sometimes think pathologists are really important, because if I'm categorizing it with incomplete information, that could have repercussions. And I take it really seriously that I'm categorizing in the best way possible with all the information I have in that moment so that my colleagues can say, okay, this is the type of surgery we're going to do. Okay, you can come back in six months and we'll look at it this time. And the other thing I really want to stress is that each biopsy or surgery is a moment in time. So we do our best work each time. And that often means that as we get more information, as we get better imaging, either because we get more information, because it's been years and years and now we just know more about you and your case. Or we get better technology. The imaging has come so so far. The different ways that we can image have come really far. So now we know way more than we did 5-10 years ago. It also means that sometimes we have to do kind of a radical re-categorization, a reassessment of our own rubric. I think people can get really upset when changes happen, like, oh, were you wrong in the past? No, everyone is just learning. And sometimes it takes a lot of courage to say, you know what, we have to change the way we grade, change the way we stage. And ultimately going forward, we now know more than we did before. So I think in 2017, a slightly updated classification of NET tumors came out. There was a lot of angst. It was actually probably ready to go about a year before it came out. But I think what it was was managing the anxiety of the pathologists, of the surgeons and of the oncologists to say nothing of the wider audience. We knew this was going to happen. One thing I would say is, if you have an older report, think about it in that way. That is the categorization and that's the information we knew at that time. So if you're looking at a report that you've got from 2004, it may look pretty different from the report that you got last week.

Lisa Yen
That's helpful. Thanks for giving us the bigger picture historical context. Taking a step back, this is really important to get to the report, but even getting to the process of the report, we get a piece of tissue from a biopsy or from surgery and it comes to you, to pathology. What type of staining should be done for NET tumors? What do you do?

Dr. Sue Chang
If we were in person I would show you. My lab staff love when I take pictures, I mean they don't love take pictures of them, but they love when I tell them who I'm showing it to. I wish you could see in our lab, there's 46 people. Just for a biopsy. They don't all do the same thing. They don't all do different things. But essentially, it takes 46 people to process all this biopsy work so that we can get you the best diagnosis. You may see buried in the fine print. Again, if you want to go and read the fine print more power to you. I love a detail so I get it. But if you never read this, don't worry. The routine stain that pathologists use is shortened to H&E, that stands for hematoxylin and esyn. And they are very old stains. They're very pretty. They're purpley blue, and like a hot pink. Pathology is very colorful. Radiologists are very jealous because pathology is so colorful and beautiful. But it's like neon pink, shades of pink and red and then like a dark purpley blue. So those are the ways that we stain the sides as a routine so that we can tell what's a nucleus, what a cell looks like, what blood looks like, it's very interesting to differentiate between them. Our human cells or not, unfortunately, hot pink and bright purple, that would be so great, but they're not. And then on top of that, you might see other reports of

things and these are more specific to NET because they tend to again, talking about grouping. Breast cancer looks different from NET. NET looks different from leukemia. They look different, and they do different things and they have different, what we call antigens on their cells. So you might see something like synaptophysin, chromogranin, a slightly newer one is called INSM1. And those are basically ways that a cell tells us, hi, I'm a neuroendocrine differentiation. I express neuroendocrine features. You don't always have to do them. I think some of the more cut and dry cases, or if you've done one more recently, and you know what's happening, you don't have to, it is very helpful, certainly for first time diagnosis, it's recommended. I'm trying not to say anything that will get anyone in trouble. The practice of pathology is fairly broad. Pathologists are all very well trained so I wouldn't worry too too much. I wouldn't call them must do checklists. It's not like you have to put on your seatbelt, it's suggested, it depends on what you've got going on, but those are ones that you may or may not see. And then I think the one that everyone wants to talk about is the Ki-67, which is a proliferation index. A Ki-67, it's an acronym, and it basically looks for cells that are in a particular stage of DNA replication. And when you have labeling of these cells, you can count them. And you can basically get a rough estimate or a reckoning of how rapidly a tumor is growing. So it's not dissimilar to how radiologists over time will see how much a tumor grows. You'll see them measure it constantly and you'll see like what was previously 1.4 centimeters is now 1.9 centimeters. This is what they're doing. Or like a PET scan, which basically looks at metabolic activity. So this is a similar idea. Different details but similar idea that basically tries to understand how rapidly a tumor is growing. And not all NETs, but most NETs use the Ki-67 as one of the criteria to figure out grading. It's not the only. We talk about it the most because people love numbers and numbers are easier to break down.

Lisa Yen
That's helpful. So typically, we would be able to find it on the pathology report.

Dr. Sue Chang
Yes. It would be probably in the fine print. Again, because what I do is I look at all of the details, I figure all this out, and then the conclusion is what I put the very top. So it's like arithmetic. I did all my work and then I circled the answer, and then I wrote the answer in the little answer slot. But if you really wanted to, you could look at all the chicken scratch and all the work that went behind it. And some people like to and some people don't. But we definitely put it all out there so that you can see it.

Lisa Yen
Thanks for simplifying all that work that you do over quite some time to one or two lines.

Dr. Sue Chang
Yes, exactly. And that's the most important thing though. If you look at that, and you walk away and say, okay, I know it's a well differentiated grade two, that's all I really wanted you to take from this, if that's all you wanted to do today. But if you're waiting at the DMV and you're like, I want to know what my Ki was, go ahead and flip to page four. Take a look at all the work that I show and how I do it. And if I added a mitotic count or not, which I think might be another thing that you might be looking for. A mitotic index is a count of how many cells that we see that are in the middle of dividing. So mitosis is the method or the description of the stages of how DNA replicates. And when you see a cell that is undergoing mitosis, that means that that cell is dividing. And the mitotic index is another factor in determining the grade of a tumor. And there are different ways to do it. Thank goodness, some people were coming up with AI, artificial intelligence ways for computers to do it. Because I had to tell you, it can be pretty mind numbing to sit there and count mitosis for a while. You just feel like it's "Where's

Waldo" sometimes. You're just looking and looking and looking. And so now there are a lot of technologies out there that help us to do a more reliable Ki-67 or mitotic index. So it's pretty exciting. Not every place does it. It's pretty high resource to set it up. But a lot of places are starting. And it's really exciting, because I think what will happen is that people even across different days can have some variation of how they do things. Me and my next door neighbor may not do everything exactly the same. We do this all the time in pathology conferences, we spend a lot of time checking we're on the same page checking, do things the same way. But you know what always is happening the same way is a computer. So that might be something in the future, hopefully, that becomes much more easily and reliably consistent. We're pretty good. But, people being people, you can't always 100% be replicating the same thing. So that's more than you want to know about the mitotic index, but I have a lot of conversations with other pathologists about AI as the big promise of the future. I think it can only help us in terms of getting consistency across the board. And I think a lot of times, what ends up happening is, the more pathology I do, the more I see variability in how people present and how pathologists think about things. At the end of the day, we're all striving to do the same thing which is to have a consistent and replicable so that we can really take population data and understand what happens. So each person's story is really important. Don't get me wrong. I really believe that. But at the end of the day, and I hear this a lot from patients, what people want is for their suffering and their trials and tribulations to mean something. And I think that all starts with data. That all starts with getting a reliable way to group people together, and then have long term population studies so that we know what all of this means. That's all I'm trying to do.

Lisa Yen
That's helpful because we want to make sure that this data is solid. All that to say that with all your work with mitotic index and Ki-67, it's all to get that bottom line to define what the differentiation and grade is.

Dr. Sue Chang
Yes. They don't always agree. I don't know if you know, but tumors, they don't like to read the textbook. They don't want to follow rules. So sometimes, not often, but sometimes the Ki-67 will seem higher than the mitotic index, or vice versa. And at that point, it's a phone call. At that point, I call my colleagues and I go, okay, this is what I see. Help me figure out which we want to go with. At some point, you have to make a decision and which one do you believe more? Sometimes the answer is we should get another biopsy, we should do some more stains. I should look at another part of the tumor and see if that tells me more. So a lot of these lead to conversations, which I think is the most important part.

Lisa Yen
Yes, collaboration and getting more data. So I'm curious, this leads into the next question, how does a tumor location play a role for what testing a pathologist might do?

Dr. Sue Chang
As we know, NETs can show up all over the body. They can show up in different ways. Occasionally, what happens is, they show up first in the liver, or they are most prominent in the liver. And at that point, primary neuroendocrine tumors of the liver are exceedingly rare. Much more likely is that there is some other primary that we have not seen yet or is very small, and we have to figure out where it came from. So a liver biopsy, for example, always sets off a search for a primary. A pancreas biopsy or a pancreatic lesion, you have to think hard, because most of the time it can be a pancreas primary. Sometimes on rare occasions, it's actually coming from somewhere else. And so the location means that you have to do a little more detective work, depending on where it is. And the other thing is that the behavior is

different. So it's well known that in the lung, there's a higher acceptable level of Ki-67 or mitotic index to still be considered a grade two. I don't think anyone is sure about why. If it's because as long as the location is special? If it's because of the physiologic in and out of air? Who knows? I don't actually have a good answer for that. But it is known that a lung NET is different from pancreas NET. And that's different from a rectal NET.

Lisa Yen
So it's really important when you get your specimens to know where it came from. I know we've been talking around these terms, so let's break it down a little bit. What specifically is tumor grade, and why is it important? And how do you determine that? I know on the patient end, there's all of these terms. How's grade different from stage?

Dr. Sue Chang
Grade and stage are cousins. They help us figure out what's going on with the family, but they're not exactly living in the same house. I don't know, this metaphor went crazy. The grade and stage are cousins. They look alike, but they do different things. Grading is what the tumor looks like. Grading is about the tumor itself. So in NETs, grading is about what it looks like and what it's expressing and what antigens are on its cell, how it decorates itself essentially, and also about mitotic index and Ki-67. So how quickly it's replicating. Those are the things that help me figure out grade. Stage is about what the tumor is doing externally. The stage is comprised of three things. The first is what we call the T stage, your tumor stage. Typically, it's about the size and the extent of involvement. There are certain size cut off. And again, all this data is because we've had decades and decades of retrospective look back and you put all the data together, and then draw somewhat arbitrary lines in the sand and say, when people have a tumor that's two cm or smaller, it looks like this. When you have a tumor that doesn't involve this organ, they do these things. So the tumor stage, typically, is about the size of the tumor and or what it involves. What portions of the GI tract it involves or a size differential. And then the N stage, it stands for nodes or lymph nodes. And that is, is this tumor anywhere else other than the original place? Is it in any lymph nodes. And again, you can have different N stages. And then the last is M stage or metastasis. We talked a little bit about liver. So if it's gone to other organs, that changes your stage. And those three things, the T, the N and the M, get put on this big table. And depending on which of these three they are, you end up with one overarching stage. So much of medicine is taking bits of information, individual data points, and then generating an overarching category based on these parameters. So your stage is often done in a collaborative way. So for example, if I'm looking at a biopsy from the lung, I don't know the M stage. I don't know the metastatic stage, but the imaging will. The imaging will pick up other things. So the proposed clinical stage for a person might be a combination of things that I say and things that the radiologist says, and maybe things that they find on physical exam. It's a group project essentially. The grading though is essentially done by pathologist. That one is me with a microscope and some stains trying to figure out which one is best graded as.

Lisa Yen
I know we already talked about Ki-67 and motitic index and what they are. How important is this [Ki-67 and motitic index] for the tumor grade?

Dr. Sue Chang
The interesting and terrible and irritating thing about working in a field that goes all over the body is that everyone's been working on it separately for a long time. So there's not one single unified grading schema which leads to some interesting conversations. The reason I'm saying this is, for example, in

the lung, the Ki-67 is actually not part of the criteria. It's suggested and I think most people do it, because you may as well. Everyone wants to know more data. I want to have all the possible help I can get before I make a grouping. But technically speaking, you don't need to use it. So if you don't see one, it's not actually like someone's not done a good job. It's just that it may not be part of the need. And also, sometimes it's not necessary, in terms of, there's so much data that you've got from all your other stains and all your other microscopic examination, that you made a categorization. I would say, it's probably less common, but I wouldn't freak out if there wasn't a Ki-67. But for all the other ones, a Ki-67, is one of the data points you actually need. And it's required in resection. Your big resections, it's a required data field there.

Lisa Yen
What is differentiation and how do you decide this?

Dr. Sue Chang
Differentiation is a feeling. And I'm sorry to say that because I sound so unscientific, but the further I get in medicine, the more I realize, so many things are a feeling or a judgment or determination that isn't black and white. So differentiation essentially is saying how well this tumor cell resembles its normal counterpart. So how far afield it's gone. Some tumors really forgot where they came from. They do not look anything like they used to, or they should. So in the NET world, there is well and poorly differentiated. There is no moderately differentiated in the NET world. In other organ systems, breast colon, adenocarcinoma, moderately differentiated is an option. But in NETs, it's fairly binary. So you have your well differentiated and you have your poorly differentiated. And those two really tend to track fairly consistently with clinical progression and survival, and stage actually. Again, they're all cousins, but they're not necessarily all living in the same household. But they do all kind of go together. So you're poorly differentiated NECs, neuroendocrine carcinomas, tend to have high Ki-67. They tend to have high mitotic index. And you're well differentiated tend to have low mitotic index. Low Ki- 67 because they're not replicating as quickly. And they tend to look, to my visual eye, more like the normal counterpart of neuroendocrine cells. Your neuroendocrine cells are all over your body all the time. They're regulating things. They're hanging out in the background, doing their thing quietly, and they look a certain way. And your well differentiated NETs, neuroendocrine tumors, can look like those guys. Just too many and in a weird place. So that's basically how I think about differentiation. One day, we should come up with a visual podcast. That's just called a lecture or webinar. If we were doing a webinar, I would put a bunch of photos up. And I think it's actually pretty obvious to everybody when you see it. One of these looks very different from the other. So if I put up a picture of a normal neuroendocrine cell, a well differentiated neuroendocrine tumor, and a poorly differentiated neuroendocrine carcinoma, you can tell one of these does not look like the other. So that's how I explain it. There's a lot of exciting development in terms of the molecular background of these. There are groups that say that if you sequence everything, you can tell the difference based on the mutations, and the driving molecular changes between well differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. That's really exciting because it means that there's a genetic reason for the things that we're seeing. And it also means, again I'm going to say, I really want as much help and information as I can get. If that means that somewhere in the future, all neuroendocrine tumors get sequenced, same as a Ki-67, it just becomes routine. That's really exciting. In terms of, it really helps us understand what's driving certain behaviors, what mutations might be sensitive to certain drugs. You just don't know. There's so many things that have changed in the field of medicine even since I went to med school. I think it's really exciting to be able to continue to understand what's going on.

Lisa Yen
Yes, we always want more data that will help. A couple other terms that come up, what does "atypical" and "typical" mean?

Dr. Sue Chang
Those pulmonary guys, they sure love their own vocabulary. So again as I said, there is no single one ruling entity that decides what is called what. So in the lung, which is also called the pulmonary system, you will see slightly different terms for the most part similarly track with the GI NETs. So typical carcinoid not exactly but basically tracks with a grade one well differentiated neuroendocrine tumor. And atypical carcinoid, typically generally, mostly has the same characteristics as a grade two well differentiate neuroendocrine tumor. So not exactly the same. Again, the mitotic count is slightly different. And the Ki- 67 can be slightly different. But the pulmonary pathologists I have actually seen now will do both. They'll give you what they call typical or atypical. And then, in parentheses, they'll write the other category, because again, we're all just trying make sure we're all saying the same thing, or speaking the same language. I've seen that come up more frequently recently, which is really helpful. So hopefully, if your listeners are seeing this, they'll see them side by side. So it's older terminology with newer terminology, and then hopefully the two, at some point, merge together, and we can just use one vocabulary.

Lisa Yen
So speaking of just trying to kind of make sense of things, can there be different grades within the same tumor or between multiple tumors?

Dr. Sue Chang
Oh, definitely. So again, pathology is so strange, because we're taking a 3D person, we're taking a little part out of a 3D person, or converting it into a 2D image. So I'll never be able to see in 2D, the full fledged 3D person, or 3D tumor, or what's going on in a three dimensional way, which is why we sample, we call it sampling. So look a little bit here, I look over there, I look all over the tumor. Maybe not all of your hair grows in the same rate. Maybe the front of your hair grows slower than the back of your head. You have to look at the whole picture together. So it's entirely possible, especially in someone who's had prior therapy and then they go to surgery or if they've had radiation in a certain portion of their body, that the Ki-67 or mitotic index looks different. And what we end up doing is looking at the highest mitotic rate and using that, because that's really the area you want to know about. And what we'll often do is, if there's a case that comes across my desk that's got a primary resection and a bunch of lymph nodes, and a lymph node NET, I'll look at all three of them and see which one's got the most aggressive behavior. It's not always the same. So sometimes you say, oh, it'll be in the liver. And it's not, it's actually in the lymph node. Or sometimes you'll say, oh, it must be in the lymph node, and it's actually in the primary site, in the small bowel. So it really depends. At the end of the day, what we end up talking about is whatever is the most aggressive, that's the part that we're the most concerned about. And that tends to be how I grade things, depending on whatever is the most aggressive.

Lisa Yen
Yeah, that's helpful. Knowing that that's the most important piece that you're ranking for the most aggressive. Throwing another curveball, how do I understand a pathology report that shows mixed neuroendocrine neoplasms?

Dr. Sue Chang
The tumors don't like to read the textbook. They really like to throw you a bunch of curveballs. One entity -- it's still in flux, actually, there's a lot of research being done. Sometimes your tumor will look like two tumors and there'll be cells right next to each other, cozied up, that look totally different from each other. And you're like, I don't understand how they can both be tumor. So there are a few different schools of thought. One school of thought is that it is actually two tumors that both got the same sort of genetic hit and just took off and became malignant. There is another school of thought that says, no, it's a tumor that portions of it have changed into a different look. So like I said in the past, chromogranin and synaptophysin are what we call expression. So it's what the outside of the cell looks like, it's what's producing. And some cells have decided, we're not going to do that anymore, we're going to make a different thing. We're going to look in a different way. We're still going to look bad, but we're going to look bad in a different bad way. And so that's actually a really complicated field and deserves a lot of attention and funding, because it can be called a mixed adenoneuroendocrine or mixed neuroendocrine non-neuroendocrine neoplasm or carcinoma. And anytime you do a mixed bag, you get mixed bad results. You get mixed bag prognoses. So it can be really difficult to prognosticate because you're not able to say with as much data or power behind it, which was the bad actor, and frankly, sometimes we're surprised by which one ends up being the bad actor. It seems to be about 50/50. I know that a lot of times people say it's the adenocarcinoma that acts more poorly. I think if you're working at a cancer center, you reserve the right to see it go the other way. And so those are mixed bags, and they're mixed knowledge too. And I think that that is one field that has recently, and will continue to get refined. And as we get to know more about what the molecular drivers are. So watch the space in terms of what we're going to do with it. It's really frustrating though. I do totally understand. It's frustrating to diagnose. It's frustrating to treat. And I'm sure it's extremely scary and frustrating to be a patient with this diagnosis. Because it's a zebra within a zebra.

Lisa Yen
Like a unicorn.

Dr. Sue Chang
It is a unicorn.

Lisa Yen
Lots of muddy waters and the need for clarity in this space. Well, the last question is, should I get a second opinion? Or better yet, when should I get a second opinion with my pathology? And if so, how's that done? And also, how long are pathology specimens typically stored?

Dr. Sue Chang
These are great questions. I love talking about this. It's not just NETs, right? So this is something I'm going to say across the board for all pathology. This will be helpful for anyone who's listening in terms of how the field of pathology, how the practice of pathology goes. Should I get a second opinion with my pathology? You know what? I have seen a lot of pathologists work come across my table as a reference cancer center. And by and large, I'm so impressed with pathologists. Like truly. Our board process is extremely rigorous. The people who practice pathology that I've had encountered with are similarly conscientious. They keep up. They teach me things. So I am by and large, incredibly impressed and confident in pathologists as a general group. I am never offended if someone asks if they can send their pathology for a second opinion. And that's why I write my reports the way I do. I assume they're gonna go somewhere else to be seen. And I want the other guy to know, like, here's all the stuff that I did. And

I think that's how we think about each other. Because when I receive an outside report and I'm looking at it, I'm always like, yep, great, sounds good, I agree with you. So it's really gratifying to get that confirmation. And here's the other thing, if I missed something, I want to know. I want you to know. And I want someone to say, hey, there's an extra piece of information out there that could be useful. So I don't get offended. Ever. And I think people are like, are you hurt? No, I'm not. You're trying to get good care for yourself and that's what I'm interested in as well. I will say that at City of Hope and not at all places, it should be at all places, but not at all places, but definitely at City of Hope, if you come to see our oncologist, if you come to see Dr. Singh for surgery, he will be sure to get your pathology reviewed here because we're going to talk about tumor board. And it's really important that he and I have a conversation about what his plan is. So he's planning a surgery based on other people's words. And I would say 97-98% of the time, I will use the exact same words. But that 2% can be really important. That 2% might mean something and certainly for "Gags" [Dr. Singh] to go in with the confidence that he's doing the right thing, that's irreplaceable. Even if it is just me saying I agree with this person, then he's got that confidence boost to say that I know this is the plan we need to do as opposed to, I'm pretty sure, or I'm sure, I hope. And if that's what it takes, then that's what it takes. I'll never mind looking at another report so that my oncologist can make the best plan and have confidence in it, or that my surgeons can make their best surgical plan and have confidence in it. So we often send out tissue because a patient has decided that they are going to another institution for their surgery. Or maybe you're moving to Florida. You retired, you're moving to Florida, congratulations. You want to set up your care down there in Florida, then ideally what would happen is that your new place that's your medical home will get to review all this stuff. And they'll say, okay, we've got the baton, and we're going to carry it forward. It's generally done by your treating oncologist or surgeon or radiation oncologist. So they basically say, I'd like to make sure that these all things are reviewed, and it's part of a startup package. You're new patient. Here are all the things that have to get checked out. All your medications have to get re-reviewed. We ask you again your surgical history, your family history, we get your pathology reviewed. I think it should be part of onboarding of a person to their new medical home. That's generally how I've seen it done. And it's probably the most effective because the people who are working at these large hospitals or clinics, it's very standard. And so there's a lot of paperwork involved.

Lisa Yen
I'm just curious, do you look at the actual slides?

Dr. Sue Chang
Yes!

Lisa Yen
The slides are sent over to you?

Dr. Sue Chang
The slides are FedExed in little protective carriers with a bunch of bubble wrap. Speaking of going digital, a lot of places are now going digital. So my great hope is that, in the future, we can do this digitally, with slides that are made into very large TIFF files, specialized TIFF files, because it means that you don't have to depend on shipping. FedEx doesn't lose things very often, but if they did, and it happened to be yours, could you imagine? There's always some anxiety about sending things out. And also it means that everyone's got a copy. You keep a copy and it's safe. Your second part of your question was how long we retain specimens? So if you're going for surgery, you might get a big portion of your liver taken out, we're not going to put the whole thing through the machine. That's too much,

and most times not necessary. So what ends up happening is that we take portions of that, we sample it and we put the rest in a container with a fixation chemical called formaldehyde. That container sticks around for about a month after we've signed out the case, just in case we had to do more things for it. The actual tissue gets processed and embedded in paraffin wax. And once it's in there, the DNA stable for decades. A very long time. The RNA, there are other portions of it that are less stable, and generally, we like to say within the past year, is the most likely to be able to do molecular testing and additional testing. But the tissue itself is stable forever, as long as you're storing them in the appropriate climate controlled area. Sometimes, it can be challenging in places like Los Angeles or Las Vegas because paraffin melts. So we're very conscientious about temperature, we actually have temperature monitors, and they alarm and go off if it gets above a certain threshold of temperature. So any laboratory has to get inspected about this. Our inspection is actually coming up, and so I'm very, very aware. But every laboratory that stores these items has to do temperature monitoring. And so that's one of the ways that we should make sure that your specimen is safe and can be used for additional testing in the years to come. There are certain laws about how long you must or can retain specimens. So it can vary depending on the hospital you're at, or the clinic you've gone to, the state that you are at. There is a minimum federally, and that's 10 years. But that's the minimum. The many places far exceed the minimum just because, certainly at City of Hope, we know that we have patients who come for decades, and we're lucky to have them for decades. And so we actually retain our specimens for as long as possible just in case something comes up and there's a new wonder drug and we want to test something from a long time ago. That's always our priority, to make sure that if you're able to use it for that patient's use, for that patient's treatment or prognosis or therapy, that's my priority. We're also a research institute, so don't get me wrong. There's always interest in using what we call archival tissue, so older tissue to promote research. And I'm very aware of that, and I believe in that. But I really have to emphasize, at the end of the day, my loyalty is to my patient. And so I will always think of that first before what we call secondary use or like additional research. I hear a lot from people who are like I really want to participate in research, but I'm concerned that it means that I won't be able to get further testing or do this thing, what if I need to go into a clinical trial? I want to assure people that I always think about you guys first. I always think about my patients first. And then if there's anything additional, or duplicative, that's when I say, okay, research, you can come on in, but it's me and you, me and you, the patient, first and foremost, at this tea party before anybody else gets to come in.

Lisa Yen
Patient-centered, we love that. So we can expect the pathology specimens to be at the institution or hospital where the surgery or biopsy was initially done?

Dr. Sue Chang
Yes and no. It turns out, space is a premium. And so as for some of our archival specimens, at least the City of Hope, it's after three years. We have them, it's off site. Again, temperature controlled, highly regulated. It's not like anyone could just like walk off the street and go get it. You think about it as like the library. Sometimes you have offsite storage of books, and they're in temperature controlled places, and you can make a request and it takes a couple of more days, but they are in our possession, just off site. So the answer is, yes, sometimes it takes a little bit longer, because we do have off site storage, but they are still tightly regulated and very secure.

Lisa Yen
I think of those like a garage storage unit where we might store things outside of our house.

Dr. Sue Chang
Exactly, much better. Temperature regulated. I don't even think most of us have access, even fewer people have access, because it's off site.

Lisa Yen
Well, thank you so much for your time. And just in closing, I just want to see if you have any final thoughts or any words of hope that you would like to share with the NET community.

Dr. Sue Chang
I just think it's so rewarding to talk with you and Lindsey and the whole LACNETS team. And anytime I get to meet patients, it's, especially for me, such a highlight, I think if you're a surgeon or an oncologist, you have clinic and you get to see people all the time. It's really gratifying for me to know that people are interested in their pathology report, and what I do and why it drives so much of the clinical decision making. And I wanted to thank you guys for holding this kind of space for both groups to be able to do it. I think it's just so important that we get to talk to each other.

Lisa Yen
Of course, and we know that it's so important. I know that our audience, our patients, we really learn what those couple of lines are that you put at the bottom of, or at the top of the pathology report, differentiation grade, we really understand that that's highly valuable and very instrumental in guiding treatment decisions. So we really appreciate all your hard work, all the attention to detail, all the hours you put in, and also all the research and the forward thinking that you're thinking about, in terms of how to make it better. And thank you also for collaborating. That's really amazing to us and it's reassuring to hear.

Dr. Sue Chang
I'm really lucky to have colleagues like Dr. Singh, Dr. Li, and Dr. Kessler to work with here. It's really fun to do collaborative research with people who get it, and who have, what I would consider, wild ideas. Like, what about this? And I'm like this is so out of the box. But this is an outside the box thinking type of tumor. And so you sometimes have to be a little bit creative and a little bit weird to try to figure out a different angle to tackle the problem.

Lisa Yen
And we appreciate that out of box creative thinking because that leads to more options and that's what we need. Thank you so much for joining us today. And we look forward to seeing you in person in the future.

Dr. Sue Chang
Gosh, I hope so! Thank you for having me. And I hope to be able to see you guys or have a conference again soon. I'm a very gestury person so I feel like we're missing all the gestures, but next time next time we see each other person, look out for all the gestures.

Lisa Yen
We look forward to it. Thank you. Thanks for listening to The LACNETS Podcast. We want to thank our podcast supporters Advance Accelerator Applications, TerSera Therapeutics, and Ipsen Pharmaceutical. For more information about neuroendocrine cancer, go to www.LACNETS.org.