



THE LACNETS PODCAST

With Gagandeep Singh, MD
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Transcription:

Lisa Yen, LACNETS Program Director 0:03

Welcome, everyone. It's great to have you to our LACNETS podcast and welcome Dr. Singh. So before we get started, I thought I'd introduce our guest speaker for today, Dr. Singh from City of Hope. He's someone that is near and dear to us here at LACNETS. Dr. Singh is the Surgical Director of the Neuroendocrine Tumor Program at City of Hope. And he is the head of the Liver and Pancreatic Surgery Program at City of Hope, as well. He's dedicated almost the last two decades to research and care of neuroendocrine tumor patients in the Southern California area. So we're really excited to have you here today with us, Dr. Singh. And if you might introduce yourself and tell us a little bit about how you got into neuroendocrine tumor care?

Dr. Gagandeep Singh 0:44

I think you said it all. You know, thank you for having me. And it's a total pleasure to be here. I look forward to the podcast and actually answering your questions, because I know there are a lot of open ended things that patients always worry about. And, you know, I think with every year, I mean, of doing neuroendocrine practice, I feel I know, much more than I used to know, even you know, a year ago. And so I think I can answer a lot of these questions fairly well. And having done this now for, like you said, almost two decades now. So let's get started.

Lisa Yen 1:24

Okay. And as our listeners know, we've been tackling the top 10 questions that are usually the ones pressing too many of us that are living and dealing with neuroendocrine tumor. And so the first question that comes up very frequently, Dr. Singh, should all neuroendocrine tumor patients have surgery?

Dr. Gagandeep Singh 1:42

First, I like the top 10 questions, like Letterman, you know, this adds a little flavor to the way these these should be answered. So I will start. So the first question is, should all patients have surgery? Actually, it's a fascinating question because neuroendocrine tumors are essentially very slow growing tumors. And I think in order to answer this question, the most important thing is, is the patient symptomatic? And if the patient's symptomatic, it's a no brainer, they should undergo a surgery. Second thing is where is the primary tumor located? Is it in the pancreas, is it in the small bowel? Is it in the colon? Is it in the rectum? Because I think there are guidelines for each that are a little bit different. And I'll get into that. And then the third part to that is do they have metastatic disease? And I think we'll probably answer that as we go along. Because I know, there's always a lot of questions regarding metastatic disease and how we should approach the primary tumor. And we've done a lot of work on that. So I'd be happy to answer those as well. And lastly, I think critical in decision making is how old are you? Now if you're somebody who is you know, 15, 20, or even 30 years old, and have a neuroendocrine

tumor that we know is going to grow with time, then I think it's absolutely necessary to operate on it before it creates problems. Whereas in the slightly older population, I don't mean older as in older you know, you were very functional today even at 70s and 80s. But you know, if you're thinking about it and you're in the 70s, and 80s, and whether you should get surgery or not, I think it is truly how big the tumor is, and how symptomatic you are is what drives decision making. So just to give an example, if I have a 30 year old patient that comes to me with a pancreatic neuroendocrine tumor, that's about 1.5 centimeter size, I know that this patient tumor is going to grow over time, and then ultimately spread to the lymph nodes and then ultimately go to the liver. Now it may take 10 years may take 15 may take 20. But we know with every thing that happens along the way. In other words, you know, with the presence of lymph nodes, your survival drops with the presence metastatic disease, your overall survival drops. So the question is, can I catch it so that I can give this patient an excellent quality of life, you know, for the next 40 to 50 years. On the other hand, if I have a tumor in a 70-year-old that's about less than one centimeter in size in the pancreas, I know for this tumor to truly become symptomatic or to become an issue, it's probably going to take 10 years or 15 years. So I would rather put that patient on surveillance and follow that rather than rushing that patient to the operating room. So it's a little bit of a balance, it's a bit of a bit of a judgment call. And I think that needs to be essentially discussed with your your physicians--the surgeon or your medical oncologist, and a decision needs to be made.

Lisa Yen 5:00

Wow, thank you for that really thorough answer. So it sounds like you're really juggling the symptoms, location, age, and ultimately the goal.

Dr. Gagandeep Singh 5:09

Correct. Absolutely correct.

Lisa Yen 5:11

Beautiful. So I guess a follow up question with that is how would I know if I'm a candidate for surgery? And if one surgeon says I'm not a candidate, would another surgeon say something different?

Dr. Gagandeep Singh 5:22

So, like I said, you know, I think you're a candidate for surgery if you're symptomatic. Now, you are absolutely right. There are two schools of thought. There are people who say, Oh, you've got a neuroendocrine tumor of the small bowel, you're not really symptomatic. And you're 65 or 70 years old, or 75 year old, and, you know, let's wait till you become symptomatic. And I'm going to give you a real example of 10 days ago, I had a patient that flew down from Portland to see me because the patient was having abdominal pain, and was diagnosed with a neuroendocrine tumor. And they had just put him in long acting, somatostatin, but he was having increasing diarrhea, increasing abdominal discomfort, and kept complaining about those things. And nobody was actually listening to him, in a way, because he was 74 years old. And that was not true. And actually, when I took him to the OR, his intestines were pre-gangrenous. In other words, it was spheric, they were almost black. And I actually told the patient and his wife afterwards I said, it was really a close call. You know, I think if you had waited even a week more, I'm not sure that he would have made it through this and you end up in the, in the ER as an emergency situation at that time. So I think it's important to consider how symptomatic you are. And a decision to make surgery is made based on that. The other question you asked is, what if one surgeon says no, and the other surgeon says, yes, I think you have to go with the feel of who you think is giving you the best options. I always believe in evidence based medicine. And I also believe in a particular physician's experience. So if you're going to somebody who's a year out in practice, and has barely seen enough neuroendocrine tumors, not that they're not good, I think they're going to get better with time. And it's a

question of maturing with decision making, go get a second opinion, and there's no harm because this is ultimately your life. And you need to know you need to take care of it, and you need to control it. So I think it is important to get another opinion if you're truly symptomatic. Now, on the other hand, you said, one surgeon says no, and there's a valid reason for saying no, for example, you're 75, you have a small neuroendocrine tumor in the pancreas, and you're completely asymptomatic. I would agree with that surgeon. So it's a balance. And I think it's a decision that you make with your team and your surgeon, again, I think it's very important to find a place and a group of doctors that are dedicated to this, so that they can help you understand what the current state of treatment is.

Lisa Yen, LACNETS Program Director 8:14

Yeah, it's complicated. There's definitely not a black and white here.

Dr. Gagandeep Singh 8:17

That is true. Yeah, there's absolutely no black and white in this. And I think it really is driven a lot by when we see the patient now, I mean, I can get a young patient, and our patients coming over from all over the country, have a two centimeter tumor and the pancreas completely asymptomatic. And you know, somebody asked them to observe it on the outside, but then the 35-40 years old, you know, it's going to grow with in time. So my recommendation to that patient is going to be surgery, because it is going to prevent it is going to give him longevity and quality of life. So it's a balance. You're right.

Lisa Yen, LACNETS Program Director 8:54

Thank you for that. So the second question is, how much control would a patient have regarding the approach and extent of surgery?

Dr. Gagandeep Singh 9:03

That's a very interesting question. So you're saying the patient have control, is that what you're saying? '

Lisa Yen, LACNETS Program Director 9:07

Yes, could they say I want to only cut certain parts, or I want it to not include this part?

Dr. Gagandeep Singh 9:15

So I think it's a it's a I think it's interesting that today's patients always get a second opinion with Dr. Google before they come to see you. And they have their own opinions. And you're absolutely right. And I think it's important to respect some of that, but you have to realize that Dr. Google is not always right. And, is not making a decision based on your presentation. He is giving you a generalized answer that's probably sometimes safe and sometimes very unsafe. So I think control is important. I think quality of life should be your main question at the end of the surgery. And third is you need to make that decision with your surgeon. And see what your surgeon's thoughts are on that. So you know, like I said again, I'm going to use a few young patients who've flown across the country because they had a tumor in the pancreas. And they were told that they need to get a distal pancreatectomy with splenectomy. In other words, a portion of pancreas needs to come out with the spleen, but they flew in purely because they didn't want to have this spleen removed, they wanted their immune system intact. And you have to convince them that, you know, sometimes it's not the right thing to do. And sometimes it is the right thing to do. And you'll find that patients sometimes are very adamant that they don't want their spleen out. And their question is, can you do it? And they'll take the responsibility. So you're right, sometimes, you'd give them the numbers, you put it in your notes. And then, in a way, they understand that we have this discussion, it shouldn't be, you know, five years from now, when they develop nodal disease, that they come back and say,

Doc, saying, you know, I didn't know better that point, and you still did the wrong thing. It shouldn't be like that. I think it should be evidence-based, it's important for them to make a conscious decision. And I do agree that sometimes I do do spleen preserving, for just those borderline lesions, for the patient's mental satisfaction. And I, of course, I always documented it so that there is no confusion, you know, five years down the line so that we know we have this discussion that this is not currently the standard of care. But it's close to giving you the same outcome that you're looking for in terms of longevity and quality of life. So you know, you have to have that discussion.

Lisa Yen, LACNETS Program Director 11:50

Thank you. So it's an open discussion.

Dr. Gagandeep Singh 11:52

It is an open discussion. It should be an open discussion. I mean, just to give you another example, I saw another patient who came from the Midwest, who was offered a total gastrectomy for a carcinoid tumor that was the removal of an entire stomach. And when he came to see me, he says, I'm going to tell you the first thing is that I like to eat. And so, he says, Can you save any of my stomach? So I said, well, let's get an endoscopy done, see what the limits are, and I think if it can be saved, yes, there's no reason to take out your entire stomach for a carcinoid or neuroendocrine tumor of the stomach. And sure enough, we were able to do a partial gastrectomy on him, which was a robotic distal gastrectomy for the patient. So, again, it's a bit of a balance. It's a bit of a discussion. And I don't give in without fully investigating the patient either. So I think it's an important discussion to be had.

Lisa Yen, LACNETS Program Director 12:45

Thank you for that. So another topic that is often on patients' minds is carcinoid crisis, as you well know. So how do you control for carcinoid crisis during surgery?

Dr. Gagandeep Singh 12:56

So we have a fairly robust, neurotic and program here at City of Hope, as you know. We're a comprehensive cancer center so they know carcinoid crisis pretty well. So every patient of mine that goes into the operating room, they already have an octreotide drip ready in the room. Whether they start the infusion or not, I leave the decision making to them. And we also know now which patients are likely to have a carcinoid crisis. So the ones that are usually likely to have a carcinoid crisis are patients who have the carcinoid syndrome. They are symptomatic neuroendocrine tumors with high levels of you know, histamine, or serotonin and stuff like that. And then lastly, a lot of the small bowel, neuroendocrine tumors that are essentially not super symptomatic, can also have carcinoid crisis in the OR. So as soon as I open the abdomen, the first thing I do is I talk to my anesthesiologist and say, I'm going to touch the tumor. And you tell me if you see anything change on your monitors, because sometimes you have a drastic drop in their blood pressure, you have a drop in their heart rate. And so you just stop right there, let him catch up, get the octreotide infusion going. And then if he needs to use a few presses to balance him out right away, usually, the anesthesiologists are so good here that they have them controlled within minutes, within 30 seconds, they're on top of it because they're already prepared for this and we prepare 100% even though the incidence is still 1 to 2% because the outcome of that can be fairly negative, if you're not prepared for it, so you need to be prepared for that. That's the key.

Lisa Yen, LACNETS Program Director 14:45

And what do you use when you're talking about preparation?

Dr. Gagandeep Singh 14:49

So the preparations really having the octreotide infusion in the operating room. That's the key is having you know, alpha pressor support in other words, having blood pressure support medicines ready to go. If the blood pressure tanks or drops at the heart rate drops, you know you have something to stimulate the heart rate, get the blood pressure up, start the octreotide infusion, and you're back in business, you're in control again, and then you proceed cautiously and see. The other thing from a surgeon's perspective, I actually like to control the blood vessels right away, if I notice that the tumor is asymptomatic, I go down to the root of the blood vessels, and I'll immediately put a clamp and divide them so that there's no further release, and then go to the rest of the dissection. And so that also help stabilize the patient. I think the other question that may be on your mind is, how long do we continue if they have a crisis in the OR? I usually move them to the ICU for 24 hours, even though I know they're not going to have any more crises after that. And I actually leave the octreotide drip on for about 24 hours, and then have them take it off in the ICU in a controlled fashion, just to make sure the patient's rock stable, and then move them out next day in the morning.

Lisa Yen, LACNETS Program Director 16:03

Wonderful. So it's like having all the tools in the toolbox and the communication and having everyone who understands how to use them.

Dr. Gagandeep Singh 16:10

Absolutely, absolutely.

Lisa Yen, LACNETS Program Director 16:12

Thank you for that answer. So the fourth question is, again, surgery related. Should all NET patients have their gallbladder removed? So if I'm someone who's living with neuroendocrine tumor, and my gallbladder wasn't removed during my initial surgery, would you recommend having another surgery to go back and have that gallbladder taken out?

Dr. Gagandeep Singh 16:31

So I know a lot of the surgeons out there recommend having the gallbladder removed. And I think it's a very great question that you asked. I think the gallbladder really needs to be removed if you are on octreotide therapy, or a somatostatin analog or on lanreotide. The reason is, your gallbladder doesn't squeeze and function like normal. So these tend to develop stones and inflammation and sludge within the gallbladder that lead to repeated episodes of right upper abdominal pain. And so if you are on octreotide therapy, or anticipate that you're going to be an octreotide therapy, then you should remove the gallbladder. Now, if I'm doing a curative surgery in a patient, once again, I'm going to go to a very tiny neuroendocrine tumor in the small intestine with very limited nodal disease. And I'm going to take it out, and you see I don't think this patient's going to need any additional treatment for 10 years, then there's no reason to take out the gallbladder, even for pancreas for that matter if you're having a curative surgery and it's just a 1.5 centimeter or 1.2 centimeter mass in the tail of the pancreas and the head, it always comes out, because that's a much bigger operations involved that always comes out with that. But in the tail of the pancreas, you don't really need to take the gallbladder out, because again, if they're not going to need additional treatment, it's not mandatory to take it out. But if you think that biologically that this patient is at some point going to need octreotide therapy, then I think it's prudent and reasonable to take the gallbladder out. So, if you've had surgery, you're not on any adjuvant therapy, or just on surveillance and your gallbladder is still there. No, you don't need to take your gallbladder out. But if you're in octreotide therapy, or as a somatostatin analog, or lanreotide, there's a 50 to 60% chance that you will develop some stones and some acute inflammation in the gallbladder and be symptomatic from it. And so you will need to probably have that gallbladder addressed at some point or the other.

Lisa Yen, LACNETS Program Director 18:41

That's helpful. Thank you. So you kind of touched on it already. So if there are already liver metastases, would you recommend having surgery? And if so, how much should be taken out? Another way to ask the question is, is there a role for taking out the primary tumor when there are liver metastases?

Dr. Gagandeep Singh 19:03

Okay, so this takes me back in time, almost 10, 12, 13 years. And you know, at that time, I didn't know enough about these tumors. We would all say, oh, this patient got a lot of liver metastases. I don't think there's any point in taking the primary out. And yet sometimes the patients who were symptomatic we would take the primary out, and suddenly we would find this patient population, doing really well, much better than the ones that we didn't take the primary out. So I actually did query this and look at this at the California level. And so we access the California cancer registry, we match the data with the clinical data of these patients who had carcinoid or neuroendocrine tumors, and then we looked at their survival. That's actually a landmark paper that was published in 2019. It was accepted in 2018. We presented in meetings before that in 2016 and 2017. But it ultimately came out in print, I think towards the end of 2019. It was in the Annals of Surgery. And it really shows that taking out the primary is one of the most beneficial things in providing longevity to the patient. Okay, now, I'm going to divide this into three different tiers. So first is, let's say you don't take out a primary, this patient is not going to do that well. If you and the patient's got liver metastases. Let's say you decide to treat the patient's liver metastasis, and not touch the primary, the patient does a little bit better. But if you take out the primary and you do the liver metastases, the survival gets markedly improved. So the more treatment you offer this patient population, the better they do in terms of longevity. The other thing is, even just taking out the primary is close to taking out the primary and doing the liver metastatic treatment. That's the best. So I don't know, I might have confused your audience. But bottom line is, I think being more aggressive is very important. Now, the second part of this question, which I think is really critical is not all patients with liver metastases can be resected. Because some patients have so much disease in the liver, that there is no way to clear the disease within the liver. So the question is, should I take out a primary? So my answer to that is going to be yes. It is definitely going to control the progression of the metastatic disease where there's something like the mothership controlling the metastases, which are these tiny satellite nodules all over, now that you've taken the mothership away, these suddenly start slowing down in their progression. The second is how much of the liver do you need to clear. So the original traditional thought process used to be that you need to clear at least 90% of the tumor burden within the liver. However, we realized today that you sometimes cannot achieve a 90% clearance based on the anatomy, the distribution of the tumors within the liver itself. So people compared 70% against 90%. And they found that the survival was equivalent. So that standard has now been dropped down to achieving 70% of the tumor burden, if you can remove within the liver, you go for it. But if you don't think you can remove if you're going to remove any 10 or 20, or 30%, there is no point in doing that. The only exception being sometimes you need a little bit of liver tissue, which you can actually get with the core biopsy. And today we are in an age of, you know, genomic analysis. So if you can do somatic mutation testing, we call it GEM ExTra here at City of Hope. But basically some somatic mutation testing on the tumor itself, I would go for that, because there are so many new targeted drugs that are being developed.

Lisa Yen, LACNETS Program Director 23:15

Wow, that was really helpful. And I thought really clear. So really, I think bottom line is, just because someone has liver metastases doesn't mean that they're not a surgical candidate. So if at all possible, cut out the mothership, and hopefully some of the satellite ships, if it's possible as well.

Dr. Gagandeep Singh 23:35

Definitely, definitely. I mean, I have patients that are actually been alive for 15 years after aggressive liver surgeries, and taking out the primaries. So 15 to 16 years that I've been doing this, so and doing well, doing well. And actually some of them without any recurrence at all. All right, the others do have recurrence, but it's okay. You know, you follow it, you have treatment strategies, you have other treatments that you put them on. So there are lots of ways that we can control itself.

Lisa Yen, LACNETS Program Director 24:08

That's helpful. Thank you for that. So going a little a step further, is there a role for surgery if there are bone metastasis?

Dr. Gagandeep Singh 24:18

So that's a big question mark. There's not enough data on that. Originally we never used to pick up the bone metastasis. But however, now with the gallium 68 scan, which is the PET scan that we do for neuroendocrine tumors, what we realized is that a lot of patients have bone metastases. And again, the data is pointing towards if these are not large, lytic lesions with symptoms, and these are very tiny scattered lesions within the bone, we tend to ignore them. And we try to presume that the patient doesn't have that bone metastasis and still go ahead and treat the primary and the metastatic burden within the liver. I don't think we will have the correct answer specifically for another 20 years. But as of now, bone metastases per se, which are asymptomatic doesn't deter us from proceeding with controlling the primary or the metastatic burden within the liver itself.

Lisa Yen, LACNETS Program Director 25:21

Okay, thank you for that. The seventh question is, what's the role of liver transplantation?

Dr. Gagandeep Singh 25:29

That's super, super controversial. And actually, even if you if you do a literature search, or what we call a PubMed search, there are very, very few articles out there. But there are a few. I was actually intrigued by this because I did do liver transplantation, the first five years of my career. But after that, I've mainly focused on resection surgeries, in other words, tumor removals, and not transplantation as much. And there's very, very limited data. So here's the issue, and I'm going to explain this, I think it's probably going to get a little bit better in the day and age of gallium 68. But 15 years ago, what we don't know and what we don't know how to predict that is their disease outside the liver when you're treating the liver itself. Okay, so the most important question is, is this liver only disease? And if it is liver only disease, perhaps liver transplantation can make a difference. But you have to understand that when you take out the old liver and you put in a new liver, you need to prevent rejection. In order to prevent rejection, you need to put this patient on immunosuppression. You have to suppress their immunity. Now, let's assume that you have a single cell or a lymph node present in the chest that you didn't know about. Now with your immunity knocked down, this carcinoid, or this neuroendocrine tumor is going to go wild because there is no immunity controlling it. And so these patients actually show up with widespread metastatic disease. Now, I don't know this for certain but you know, Steve Jobs, underwent a liver transplantation in the liver, but really didn't benefit from it because he succumbed within a year to year and a half from the neuroendocrine tumor itself. And, again, without knowing his records, I think it's impossible to say, but my only guess is that that's probably what happened in that sort of a situation there. But when you look at the limited series, there's a 40 to 50%, five year survival in this patient population. But I think in this day and age can be controlled with something else is the question I would ask first.

Lisa Yen, LACNETS Program Director 27:49

Okay, thank you for that-- taking on a controversial question. So Dr. Singh, the eighth question is, what are the risks of scar tissues for multiple surgeries? And what can be done about it? I guess another kind of sub question within that is how many surgeries could a body handle?

Dr. Gagandeep Singh 28:09

Again, that's an interesting question as well. So every surgery has scar tissue. So I'm going to draw an analogy here. Let's say you get an incision on your arm for something, or let's say for a muscle repair, or whatever it is, or somebody gets knee surgery, you have an incision, they put a new joint in, remember that incision is always going to remain. So the incision heals with scar tissue. Scar tissue is basically collagen. It's dense, normal tissue, but far more dense, because it's trying to hold on to the other edges of it. Now you can go to a plastic surgeon and have him excised the scar, but it's still going to heal with a scar. Okay, so there is no absolute way to get rid of scar tissue period. So every surgery is associated with scar tissue. Especially with the abdominal surgeries, you mobilize the intestines, you take them off their roots, you take them off their normal connections, when you put them back there is going to be scar tissue. Your abdominal incision just to enter into the belly. Whether you do laparoscopic, open or robotic, the amount of scar tissue is going to be less because it's going to be based on the size of the incision, but there's still going to be scar tissue. There are some populations, some ethnic groups that developed far more scar tissue than other ethnic groups that develop less scar tissue. We don't know the exact reason for that. So scar tissue is one of those things that actually cannot be avoided. It's always going to develop. Now, for abdominal surgeries, especially for the colon and rectal surgeries. They had developed something called the seprafilm, which is a thin, collagen preventing sheet that a lot of the colorectal surgeons used to put in when they closed the belly because they knew the intestines are going to get scarred in and some are going to go into the pelvis and cross combat, some kind of obstruction, etc, etc. There's a mixed bag on that, I think, you know, a lot of the colorectal surgeons 20 years ago use it like water so everybody was putting it in. But today, less and less people put it in because we realize that you still develop scar tissue. Some develop dense, some develop less, and it's difficult to quantify the amount of scar tissue. Your last question, which was, how many times can you have surgery? Well, you can always have surgery. I think it just gets harder and harder every time you go into the belly because there's always more and more scar tissue. Now, one interesting fact, which is important for I think to know in terms of scar tissue, let's say you had surgery when you were 20 years old, and now you're having surgery at 50 years old, the scar tissue becomes thinner and thinner and easier to work through than having surgery, say one year apart from the previous surgery, that's always more dense. If you're having surgery within the two years, that's always far more dense scar tissue. But the further you are from the primary surgery, the scar tissue tends to be easier to work through rather than being as dense as one would have it in a short intervals.

Lisa Yen, LACNETS Program Director 31:29

That's helpful because you know, as people are living longer and longer and wondering, okay, well, I had several surgery, but it was, you know, 10-15 years ago, could I have surgery again, it's possibly something they could revisit.

Dr. Gagandeep Singh 31:43

Right, right.

Lisa Yen, LACNETS Program Director 31:46

So the second to last question is what's the role of adjuvant therapy for NET, and if you could explain what that is?

Dr. Gagandeep Singh 31:53

So adjuvant therapy, means additional therapy. So the term adjuvant is actually coined to prevent recurrence. But in the NET community, we also use the word loosely, also to prevent progression. Because you have patients who get adjuvant long acting somatostatin, lanreotide or octreotide, because they have liver metastases after the primary has been removed. And people refer to that as an adjuvant therapy too, but technically, that's not adjuvant. Let's say I did the small bowel surgery, there is no additional tumor inside the belly. And I'm using an agent to prevent recurrence. At the present time, the role of adjuvant therapy is limited. So again, I'm going to use an example to explain this to you. So I had a patient that was young and underwent a total pancreatectomy with liver resection for liver metastatic disease about 12 or 13 years ago. And when this patient underwent the resection, the mother obviously I mean, she was in 20s. At that time, the mother said, Well, you know, what can we do to prevent it from growing back and I said, you know, right now, there are no cancer drugs that really do work. We can use the following. at that time, we had capecitabine and temozolomide to prevent it. But I said, Why don't we get opinions of the medical oncologist and again, the medical oncologist does not know too much about it, at this point too. So, the patient and the family actually made three trips, I made a few phone calls to the Midwest to the east coast. And the bottom line, the question that all medical oncologist, is their disease that you can measure today? If there is no disease that you can measure today, then there is no role for adjuvant therapy. So in other words, because there are no liver metastases today, and there is no primary today, giving octreotide therapy or lanreotide therapy or any kind of you know, mTOR inhibition or whatever you want to, there's no data to support that. You need to have measurable disease within the body to receive adjuvant therapy. So if I took out the primary and does still liver metastases there, then that patient qualifies for adjuvant therapy. Does that make sense? I know it's a little bit confusing here. But that's what adjuvant therapy is. And of course neoadjuvant means prior to the surgery before going into the operating room, that you were given something aggressive in terms of chemotherapy to reduce the size of the tumor, so that you could operate on this now it's actually more important than the terminologies in more aggressive cancer that we go into the operating room for. But for neuroendocrine it's a little bit of a gray word. It doesn't have exact boundaries.

Lisa Yen, LACNETS Program Director 35:07

Yeah, thank you for that, that really clear explanation of the definitions and their roles. And the last but not least question is what treatment or other development in this field are you most excited about? And in closing, what kind of hope might you offer to those living with neuroendocrine tumor or their loved ones?

Dr. Gagandeep Singh 35:27

So, first thing I'm going to say is always think positive. Second thing, we could have been dead from the pandemic and we're here, and we're listening to this podcast. So I say you have something to be thankful for right there. So let's not worry about the neuroendocrine tumor, that is not going to be the cause for your demise. So it is developing a mindset. I think the most important thing is developing a mindset where sometimes you've gotten around to consumers, but living with it and enjoying the moment. I think that is key. That's what we've got to realize with neuroendocrine tumors often, that is not the tumor that's going to kill us. Yes, sometimes it does progress to point, but that is something that we need to live with that positivity and just go about with life in a daily fashion, even though you know that you've got something that's going on. But don't worry about it, I think being positive is very important. Lastly, asking about what's on the landscape, there are a lot of targeted agents that are being developed. We ourselves, actually have been working for 10 years, I've been working with John Williams. And now with Dan Li, developing a two or three different types of targeted agents. Unfortunately, we're limited by two very important things. One of the biggest problems we have

is that the cell lines that we use in vitro, don't behave like the tumors behave in vivo. And they lose their so called somatostatin receptor activity with every passage of the cell line. So we haven't been that lucky in being able to control these tumors in a petri dish. On the other hand, if you can't control these on a petri dish, when you convert them into an animal model, it is even harder. Although there are now in your animal models that were focusing the design on the molecule to work on, rather than working exclusively in the petri dish that I think is very, very encouraging. And then as you know, City of Hope is actually the home of CAR T-cell therapy, which is immunotherapy in a way. I think if we can hone in and harness our own immune therapy going forward, that is going to change the landscape. So I'm very optimistic. I know I don't have a clear cut answer today for it, but I'm so optimistic that I'm hoping that in five years, we do have an answer for it. So in conclusion, what I would say, learn to live, learn to fly with it, and without worrying about it. Thank you very much.

Lisa Yen, LACNETS Program Director 38:13

Thank you so much, Dr. Singh. Your hope and optimism is so contagious. And this has been such a fun conversation. We've learned so much. I'm really confident that everyone's gonna get a lot out of this. And we're just very appreciative for all your hard work for you and your colleagues. Because of your hard work and dedication, we can have the hope and optimism and learn to focus on not just the treatment and surgeries, that's all a means to the end, the means to the end goal, which is to live life like you said,

Dr. Gagandeep Singh 38:46

Right. Thank you for having me. It was a pleasure to do this. So thank you again.

Lisa Yen, LACNETS Program Director 38:51

Thank you so much, and best of luck to you.

Dr. Gagandeep Singh 38:54

Bye now. Bye.