NETWise
A Podcast About Neuroendocrine Cancer

Episode 35:
Histotripsy
Transcript

If you're new to NETWise, we strongly recommend you go back and listen to the first episode in this series. It goes over the basics of neuroendocrine tumors and how they're treated. And you can find a whole library of episodes on different topics at netrf.org/podcast, where you'll also find infographics and videos that expand on this material.

If you have a story to tell about your own NET journey, please email us and let us know – podcast@netrf.org

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Mary Seibert is a professional opera singer, so she pays pretty close attention to her body. She works to take good care of herself, eating well and getting lots of exercise. But for years, she experienced this occasional pain under her ribcage.

> ***Siebert:*** *And I assumed it was some sort of food sensitivity because it would go away. And about a year ago in April, I experienced that same intense pain under my right rib cage, but it remained there for five hours.*
>
> *And so I went to my doctor, had a scan, discovered a pancreatic tumor, was misdiagnosed with adenocarcinoma. And my second opinion doctor diagnosed neuroendocrine tumor*

She had a distal pancreatectomy and a splenectomy in May, and it seemed like everything was going to be fine after that -- the surgeon was confident he'd gotten all the tumor.

> ***Siebert:*** *No more anything. I wouldn't have radiation. I wouldn't have chemo. But when I went four months later for my scan, just to check how things were going, we found what they're calling innumerable tumors in my liver. So a lot of small ones that are scattered all through my liver. Those tumors in my liver appear to be inoperable.*

Her oncologist put her on CapTem chemotherapy. And then he mentioned a brand new procedure, called "histotripsy." She learned that it was a noninvasive, new technology that destroyed tumors using ultrasound.

> ***Siebert:*** *When I heard it was non-invasive and used sound waves, as a musician, I thought that's the way to-- that's the way to go!*

In the past few months, there's been a lot of buzz in the NET community about histotripsy. This newly-approved procedure holds a lot of promise for treating NETs, and may prove to be even more exciting in the future.

I'm Jessica Thomas, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

In today's episode of NETwise, we're going to tell you everything we know about this new treatment: how it works, how it came to be, and what it means for NET patients.

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Mary Seibert learned about histotripsy in late 2023, right after the U.S. Food and Drug Administration approved it for the treatment of liver tumors. This is exciting for NET patients, because the liver is one of the most common places where NETs metastasize.

The procedure is quick, non-invasive, and very precise.

But before we get any further, we want to explain what exactly histotripsy is.

> ***Ahmed:*** *It's a way to treat tumors using ultrasound energy.*

Dr. Osman Ahmed -- who goes by Dr. Os -- is an interventional radiologist at the University of Chicago.

> ***Ahmed:*** *Not sure how many people know what interventional radiologists are, what they do, but, um, do a lot of different things, basically using CT scans or ultrasounds to actually guide us to do procedures. So we do a variety of things, but one of my main focuses is treating cancer patients.*

Dr. Os is among the first radiologists to use histotripsy to treat tumors. He explains how the procedure works:

> ***Ahmed:*** *Imagine like a photocopy machine that has this like robotic arm attached to it that has an ultrasound machine in it. So we actually use the ultrasound to identify the tumor or find the tumor in the liver. And then we just sort of draw a circle around it.*
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> *At that point, the rest of it's basically done on the computer. So on the actual machine part of it, the photocopy side of it, we just put those inputs in there. And then at that point, the ultrasound does its thing.*

What the ultrasound does is send short, intense bursts of sound waves into the tumor, which destroy it.

The procedure is noninvasive – nothing breaks through the patient's skin. There are no incisions, no needles, nothing. When it's over, a patient can pretty much get up and walk away. Over the next several weeks, the body will flush out the destroyed tumor tissue. This is one of the main things that sets histotripsy apart from other procedures, and what makes it attractive to many patients.

> ***Ahmed:*** *You know, we have a lot of new technology, which we're very blessed with. But this is sort of really paradigm-shifting technology because it's so, so new and so different.*

But how exactly does it destroy the tumor? To understand that, first we need to understand what an ultrasound is.

"Ultrasound" refers to a high frequency of sound that humans can't hear. Just like the kinds of sound we CAN hear, ultrasound waves bounce back when they hit something hard or dense. An ultrasound device sends these waves into the body, and a computer creates an image using the waves that bounce back. This allows us to see physical structures inside the body. It's similar to the way bats use echolocation to "see" what's around them.

Doctors use ultrasound to check on pregnancies, examine breast lumps, and diagnose gallbladder disease, among other things. It is entirely safe, and does not destroy tissue. But histotripsy takes ultrasound a step further:

> ***Ahmed:*** *Instead of just using the ultrasound to visualize the tumor, it actually creates really short but high bursts of ultrasonic energy that are such high energy, they create little micro bubbles in the tumor. And that actually sort of blasts the tumor away.*

The technical term for this is "acoustic cavitation." It works because there are tiny air bubbles all throughout the body -- like in our blood, and in our tissue. A high-intensity ultrasound wave causes these bubbles to expand and collapse, breaking down tissue.

The histotripsy machine uses a normal ultrasound to identify the tumor, and then cranks up the soundwaves headed to just that one specific area. This destroys the tumor.

This is also where the name "histotripsy" comes from. The word combines the Greek roots "histo" meaning "soft tissue," and "tripsy" meaning "mechanical breakdown."

> ***Xu:*** *Many people afterwards complain that it's such a tongue twister, it's not easy to pronounce, but, really, we thought mechanical breakdown of soft tissue, that's exactly what the technology is.*

This is Dr. Zhen Xu. She's one of the inventors of histotripsy, and one of the founders of HistoSonics, the company that makes histotripsy devices. She's a professor of biomedical engineering, radiology, and neurosurgery at the University of Michigan.

> ***Xu:*** *And my research focuses on developing non invasive intervention for cancer, cardiovascular disease and neurological diseases.*

The idea of histotripsy first came up in the early 2000s. At the time, it was thought that using ultrasound to perform a high-precision surgery was impossible.

> ***Xu:*** *But we thought, why don't we give it a try, right? Although we had no clue where to start at the beginning, but it seemed to be, at least in theory, a possibility.*

It took many months, and hundreds of failed attempts, but eventually, they had a breakthrough. One day in the lab, Dr. Xu tried using a much higher frequency ultrasound than she had used previously, and she noticed that it was destroying tissue in a way she could control.

> ***Xu:*** *And I thought I was dreaming. And I moved a position, I tried it again. And the same thing happened. And after the third time, I was like, Oh my god, this is real.*

This was back in 2002. They spent the next ten years figuring out how exactly the mechanism worked, and developing tools to perform the procedure.

> ***Xu:*** *Then another 10 years to investigate using histotripsy for specific clinical applications so that we can do preclinical studies followed by clinical trials and eventually through the FDA to get FDA approval.*

So how does this new procedure fit into the landscape of treatment options already available to NET patients?

Neuroendocrine tumors can be treated in many different ways, depending on their stage, grade, location, and several other factors. But there are two treatments similar to histotripsy that are commonly used to treat liver tumors. These are ablation and embolization.

Ablation is when a needle is inserted into a tumor, and then the tumor is either burned, frozen, or electrocuted.

> ***Ahmed:*** *And they're called like, microwave ablation, cryoablation, or electroporation. Those are sort of the- the major types. But effectively, the concept is the same: taking a needle, sticking it into the tumor and blasting it away.*

Embolization is when a small tube is inserted through an artery and used to deliver medication.

> ***Ahmed:*** *So for cancer, we can deliver radiation beads. We can deliver beads soaked with chemotherapy. Or we can just deliver beads themselves. Typically for our neuroendocrine patients, we just deliver the beads themselves. That's called bland embolization.*
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> *And the two therapies – ablation and embolization – those are very complementary in that, if you have a few tumors, one or two tumors, then we do ablation. Because otherwise it's very time-consuming to put a needle into 40 different tumors if you have many of them.*
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> *So that's sort of like – in a war analogy – like the sniper, we go in and we try to, you know, try to kill one tumor. But if you have multiple tumors, it just doesn't make sense. So the bland embolization makes more sense. That's more like you're, sort of like, you know, you're dropping a bomb over a whole large area, you know? And so that's very effective for, for patients who have, a ton of tumors, like 15, 20 tumors.*

Between these two treatments, histotripsy is more similar to ablation. But there are a few key traits that set it apart. First, like we mentioned earlier, it's a noninvasive procedure.

> ***Ahmed:*** *So even an ablation, it's a very small needle. But it's still invasive, right? Still involves breaking the skin. So histotripsy is completely non invasive. So the ultrasound goes over the body, but, but nothing actually enters. Nothing breaks the skin. So there's a lot of excitement because we're sort of transitioning from minimally invasive to non invasive, which is always good for our patients if we can be as little, or not invasive as possible.*

The second trait that sets histotripsy apart from other treatments is that it's non-thermal.

> ***Ahmed:*** *So, we talked about how ablation- most ablation we use is thermal. So we are burning - usually it's burning - so we're usually burning tumors. The good thing about burning tumors is very effective. It kills tumors. It's like, it's almost like it's, it's about as close to having surgery as possible. So we, that's why we like to burn tumors if we can.*
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> *But burning tumors is limited by proximity of the tumor to critical structures. So if the tumor is very close to a blood vessel, for example, we a lot of times can't do ablation. We can't put the needle in there because we don't want to burn the artery or vein that's close to it. And unfortunately, the liver has a lot of those.*
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> *And/or there's something called the "heat sink effect." Meaning the blood actually in the blood vessel carries the heat away. So imagine you're trying to burn the tumor, but the artery right next to it is actually carrying that heat away. So you get incomplete ablations.*

Because histotripsy is non-thermal, it isn't affected by blood vessels. In addition, the high precision of histotripsy allows blood vessels to be preserved, even if they are close to a tumor.

> ***Ahmed:*** *So you can, go right up to a blood vessel. You can actually draw a circle around a blood vessel. Like we treated one patient where the blood vessels actually started going through the tumor, and we did the histotripsy and on the follow-up scan, you can actually see that there's the vein, the vein is still preserved. So it like sort of carved out a circle around it.*

Finally, one of the most exciting qualities of histotripsy is that it appears to prompt an immune response. This has to do with the fact that unlike other treatments that use radiation, chemotherapy drugs, or heat, histotripsy just breaks the tumor apart. Remember, the "tripsy" part of the word means "mechanical breakdown."

> ***Xu:*** *We're still trying to understand the mechanism behind it. But, histotripsy mechanically disrupts a cell membrane, but it does not damage tumor antigen. So it actually helps release tumor antigen, which is the first step to tell the body, "Hey, cancer is attacking." And then really stimulate the body's immune system to act.*

In other words, when the body is cleaning up the tiny pieces of the broken-up tumor, it recognizes them as a threat. And because the tumor cells have not been altered by heat or radiation, the immune system can then potentially recognize and target other tumors.

This opens up the possibility of using histotripsy in combination with immunotherapy, with the hope that it could bring about even better results.

But this is still in the early stages of research.

> ***Ahmed:*** *It's still theoretical. There's some animal data. There's a lot of, you know, sort of, what we call preclinical studies or animal studies. That strongly suggests this. But we're still far away from that. So, I get a lot of messages from people asking about that, and I share their enthusiasm. But I think we're still a ways from sort of, you know, getting that information.*

Up to this point, we've only been talking about tumors in the liver, since that's what histotripsy has been approved to treat by the FDA. This is exciting for NET patients, because the liver is such a common organ for metastases. But as we know, NETs can occur throughout the body. So something else that's exciting is the idea that histotripsy could one day be used on other organs as well.

> ***Xu:*** *Even though right now histotripsy is only approved by FDA to treat liver tumors, it is a platform technology that can be used for a wide range of applications, including other types of tumors and, you know, logical diseases and cardiovascular diseases. So we are actually expanding, histotripsy to applications beyond liver tumors.*

According to Dr. Xu, there is currently an international clinical trial underway looking at histotripsy to treat tumors in the kidneys. They are also beginning to look at using histotripsy in the pancreas.

> ***Ahmed:*** *You know, the surgery to treat pancreatic cancer, you basically take out everything in the abdomen. It's like one of the most, you know, morbid surgeries called the Whipple procedure, where you have to take out a lot of intestine and that sort of stuff.*
>
> *So, if you can like robotically draw a circle around the cancer and then do this noninvasively, that would be a game changer, you know? So, I think using that technology for other types of tumors, I think we'll, we'll, we'll*

see it really hopefully start gaining use for a lot of other things.

Xu: *So there's just so many things that we don't know yet, and who knows, right? Histotripsy may be the beginning of a new era. Where research on, this type of approach can push the medicine in a new direction.*

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New research is exciting, but let's take a step back and look at what this treatment option actually looks like for NET patients. Here's what you should know:

First: as of now, histotripsy is limited to the treatment of liver tumors.

Second: not all patients with liver tumors are good candidates for histotripsy. Similar to ablation, it's best-suited for patients with just a few tumors that can be identified clearly with the ultrasound.

Ahmed: *I think if you have, you know, 1, 2, maybe 3 tumors, in your liver, then I think we could evaluate you. I think if you have multiple tumors, I would say just hang tight, don't give up. But, we still need to get some trials started. Some studies started where it may make sense to sort of, then use histotripsy for those, and, and we're a little bit away from that.*

Third: histotripsy is most successful in treating tumors that are up to 3 centimeters in diameter.

Ahmed: *So for a tumor that's three centimeters or less, and we're doing histotripsy for it, just like if we're doing ablation for it, I would counsel that patient we're going in to kill this tumor a hundred percent.*

> *The larger it gets, the time to treat sort of goes up exponentially. So to treat tumors larger than three centimeters does take a lot longer, just like with ablation. And also the effectiveness goes down. So once you get beyond three centimeters, the chance of residual tumor left behind or tumor coming back. Recurrent tumor does go up.*

Even if you are a good candidate for histotripsy, there are other challenges that may arise.

For one, there isn't a histotripsy machine at every hospital. They are extremely expensive, and still very new. This means that right now, they are few and far between.

Another challenge patients may run into is with insurance. With any new treatment, it can take an insurance company a while to accept its legitimacy. And even then, there still may be many hoops to jump through.

Ultimately, it's up to you as the patient to decide what kind of treatment you pursue. If you and your doctors have determined that histotripsy is the right option for you, don't give up. And if it doesn't sound like the right option, that's ok too.

> ***Ahmed:*** *There's always going to be different types of patients. You're going to have patients who want the newest and greatest technology. But then you'll always have patients that say, 'Okay, well, I want what's tried and true.' And so obviously histotripsy probably wouldn't make as much sense for somebody like that because of how new it is and our sort of attempts to understand what its ability and potential is.*

Basically, histotripsy is a new tool in the toolbox. The hope is that the technology will expand to have many more applications, but right now, we're still at the beginning.

For Mary Seibert, histotripsy is the right thing to do, even though it won't be curative. She has lots of small tumors in her liver, but her doctors think histotripsy could be an effective way to reduce the tumor burden.

> ***Siebert:*** *Unlike drug treatment, it's not going to wash through every tumor I have and have an effect on all of them. It'll be the ones he can actually target,, so I'm concerned about that, but I'm, I'm definitely excited to learn more about it, to experience it, and I'm very hopeful.*

She anticipates she may have to make return trips for future procedures -- but that sounds a lot easier than going through another big surgery.

> ***Siebert:*** *It was no fun recovering from that pancreatectomy and I'm- I'm healthy and strong, but it was painful. It was a long time. It had so many possibilities to go awry. The idea of being able to use a non-toxic procedure that doesn't require painful recovery and lets me go back about my life the next day is like a Star Trek wonderland.*

Mary's histotripsy is scheduled for late June. She hopes that after it's over, she'll be able to enjoy the rest of the summer ahead.

> ***Siebert:*** *You know, it's really scary to have cancer. And yet this is so interesting that it's exciting. It's exciting because it has the potential for healing, but it's also just, you know, an amazing discovery and it's exciting to maybe have the chance of being part of it.*

Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education for the NET Research Foundation.

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Special thanks to everyone we interviewed for this episode. We are grateful for your expertise.

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