

Novel Approaches for Patients with Neuroendocrine Tumors Using Radiation Microspheres

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Introduction

Andrew Schorr:

You may have never heard of neuroendocrine tumors or carcinoid tumors. These cancers are being treated now with highly effective targeted therapies. They're really jumping leaps and bounds in the treatment of rare cancers and tumors that show up in the liver. Coming up you'll hear from Dr. Riad Salem about these treatments including a success story from his inspiring patient, Eva Donaghue.

Hello and welcome to Patient Power sponsored by Northwestern Memorial Hospital. I'm Andrew Schorr.

Well, on our programs we discuss a wide variety of illnesses, and there are some that are common and some that are much more rare. When you talk about tumors to the liver, and we're going to talk first about one particular kind that can spread to the liver, carcinoid tumors, this is not common, but it can be quite serious. And there have been a variety of drug approaches, chemotherapy approaches, surgery sometimes can be done. But what if you can do it in a much less invasive way, a much more targeted way? Well, that's what we're going to talk about today with a leading interventional radiologist, and we'll help you understand what an interventional radiologist does, but first let's talk, as we always do, we begin with someone who has benefitted from this approach, someone who is maybe alive today because of the improvements in medicine.

Eva's Story

Andrew Schorr:

So I want to introduce you to Eva Donaghue who is 60 years old from Arlington Heights, Illinois, just outside Chicago. Eva, welcome. So Eva, I know it's been a difficult few years for you now. I think, was it in 2006 you thought you had IBS and then you had terrible pain, and when they did a laparoscopic procedure to see if there was some kind of adhesions or something going on in the abdomen that they could fix at your community hospital, they found what in the liver?

Eva:

They found a lot of tumors on the liver.

Andrew Schorr:

This must have been a tremendous shock.

Eva:

It was quite a shock, yes. In fact, the surgeons who performed the surgery originally told me as we discussed the surgery and I asked about the potential for cancer, I remember him saying to me, Eva, I will be shocked if you have cancer.

Andrew Schorr:

So you were all shocked. So you eventually connected with Northwestern.

Eva:

I did.

Andrew Schorr:

And a leading medical oncologist there, Dr. Al Benson. And that led to, well, first the discovery that these were these rare tumors, right, carcinoid tumors?

Eva:

Yes.

Andrew Schorr:

And so you were given what is often for that, I think. It's a drug, Sandostatin injections.

Eva:

It is.

Andrew Schorr:

Trying to keep those tumors at bay, but you still had a lot of pain.

Eva:

Yes. I continued to have a lot of pain, and the Sandostatin injections often helped the symptoms, and I was very fortunate in the fact that I did not have regular carcinoid-like symptoms, but I did continue to have this chronic pain.

Andrew Schorr:

So they looked around and they found there was actually some sort of obstruction in your intestine, some tumor in the intestines where maybe this all began?

Eva:

Exactly. After being persistent about the fact that this pain had to be something that needed to be taken care of, we did talk with a doctor at Northwestern about having an endoscopy capsule. And that takes photo images.

Andrew Schorr:

Right. People often have it for Crohn's disease. You swallow this camera, it goes through your whole digestive tract. So I understand they have a little test capsule to see. What happened?

Eva:

They did. It did not make it through the digestive tract.

Andrew Schorr:

So there was a blockage.

Eva:

So then we realized we had to go forward and have surgery and find what the blockage was. And on Valentine's Day, 2006 Dr. Wayne at Northwestern Memorial Hospital performed that surgery, and the primary tumor we suspect was found there that day in the terminal ileum, and 20 inches of my small intestine was removed on each side of that blockage.

Andrew Schorr:

So 40 inches or so.

Eva:

Yes.

Andrew Schorr:

So that takes care of the pain, and you were feeling better.

Eva:

Right.

Andrew Schorr:

Feeling good, and you were working?

Eva:

Oh, yes.

Andrew Schorr:

But there was this little problem of all those tumors that were found originally when you thought you were being treated for irritable bowel syndrome. So what do you do about that?

Eva:

Well, we continued on the Sandostatin, but the tumors did increase in size on the liver, and the bilirubin count was increasing. So that's when we consulted with Dr. Salem.

What is Interventional Radiology?

Andrew Schorr:

All right. We're going to meet him in just a second. So the idea is that you were feeling pretty good but the numbers were going in the wrong direction and you knew you needed further treatment and so the question was what. Well, that really is the subject of our program today as we learn about what are some of the latest options really in targeted therapy delivered right to where the tumors are and what illnesses those can help, like Eva's.

And that brings me to introduce you to Dr. Riad Salem. Dr. Salem is an interventional radiologist, and he'll explain what that is. He's the director of interventional oncology at the Robert H. Lurie Comprehensive Cancer Center at Northwestern University and Northwestern Memorial Hospital. Dr. Salem, thank you so much for being with us. Why don't we just start with the very basic. What's an interventional radiologist? Most people think radiologists, you know, worry about x-rays and MRIs, maybe ultrasound, but interventional, what does that mean?

Dr. Salem:

Well, first of all, thank you for having me on the program today. It's really a pleasure to be here and an honor to be here with Eva. An interventional radiologist is a subspecialty of radiology that is involved in image-guided therapy or minimally invasive treatments. If you think about minimally invasive procedures in medicine this is what interventional radiologists have been doing for 25, 30 years, using image guidance to perform minimally invasive surgeries. The easiest one people think of is an angioplasty. Angioplasties have been done by interventional radiologists, have been done for a long time, and now we have expanded these minimally invasive concepts to the treatment of cancers, to doing other procedures, to decompress obstructions, perform biopsies, etc. So it really has grown into a very large subspecialty of radiology.

Andrew Schorr:

All right. Now, Eva comes to you and she has tumors on her liver. I think, Eva, you told me over the phone it was like spread, like holes in Swiss cheese, maybe 20 to 40 tumors in your liver.

Eva:

Throughout the liver, yes.

The Latest Technology: Targeted Therapy

Andrew Schorr:

Throughout. And, Doctor, of course there are other people maybe with liver cancer it's more specific, but in either case, and we'll discuss all that, interventional radiology now has an approach where you can go up through a catheter, I think through the groin and people, many people are familiar with angioplasty that you

mentioned where you go up through the groin as well, but you're headed to the liver. So what are you able to do now with the latest technology? Help us understand that.

Dr. Salem:

And that's correct. What we do is we perform these procedures through the groin. The artery of the groin is connected to the large artery of the body called the aorta, and that is connected to the arteries to the liver. And what we do is we catheterize these areas and we inject a contrast because one of the principles of liver tumors is that their blood supply is derived from the artery, and if we inject the artery with a therapeutic product, a therapeutic device, say chemotherapy, say radiation microspheres, the subject of today's discussion, then because tumors have a lot of blood flow these therapies get absorbed preferentially in the tumor, and this is where the therapy itself focuses, concentrates and does what it's supposed to do. If it's a chemotherapy it kills tumor cells by the chemotherapeutic effect. If it's radiation then it kills tumor cells by irradiation. But this is the principle, is that the blood supply being preferentially supplied by the artery, so we capitalize on that mechanism. We take advantage of that to try to target the liver tumors.

Andrew Schorr:

But in this age of targeted therapy, so the idea is rather than giving you a drug that goes throughout your whole body or radiation that's more broad that's delivered externally, you want to get it right to where the tumor is and where the blood supply is to that tumor.

Dr. Salem:

That is correct. That is exactly the approach that we have taken. Indeed, systemic treatments, as you mention, go through your body and via different mechanisms may or may not concentrate in the area of disease. In this case we are injecting--when we are working in the liver we are injecting our therapeutic agent directly in the liver so it stays in the liver, so it's extremely focused.

Andrew Schorr:

All right. And the idea is also these procedures can often be done as outpatient, and the side effects may be much less, correct?

Dr. Salem:

Yes. In fact if we focus now a little bit about the radiation microspheres, all of these procedures are done as outpatients, which I believe is an area of significant advantage over other therapies because patients go home on the same day. When patients come in for the initial testing part with the angiography they usually are with us between four and six hours, but on the day of treatment the patients are with us for two hours, and they are home in the early afternoon or so. So it's very, very convenient. And because of our ability to, or I should say the lack of significant side effects is what really permits us to perform this as an outpatient.

Andrew Schorr:

Let's hear Eva's experience. So, Eva, you're referred to Dr. Salem.

Eva:

Yes.

Andrew Schorr:

And he discussed with you whether or not you're a candidate or whether they should investigate further whether you could have this targeted approach. So how did it sound to you that possibly they could go up through your groin and treat the tumors right where they are other than some other big surgery, if that were even possible, or a lot of drugs that would go throughout your body?

Eva:

I was very excited about the whole opportunity. I did a lot of research. This targeted therapy, minimally invasive with few side effects just really fit my specific needs perfectly.

Andrew Schorr:

Dr. Salem, so let's understand a little more. So I understand Eva came to you and it was kind of a three step process. First, mapping, right, Eva, taking a look at basically the vasculature of the liver and then first treatment with these microspheres we're going to hear about to one lobe of the liver and then the other. So, first of all, this mapping, Doctor, we wonder, well, who is a candidate for this targeted radiation interventional procedure, and when would it maybe not be such a good idea?

Dr. Salem:

So we are very fortunate here at Northwestern that we have a very rich experience with this therapy. We have been doing this for many years now, and personally myself over ten years now and treated well over a thousand patients now. So we are able to select and identify patients that I believe would benefit most in the clinical arena. So after discussion, looking at the history, assessing the films, the blood tests, the lab tests, etc., we are pretty good at telling who would be a good candidate.

People that would not be good candidates are those where there is liver dysfunction, so unfortunately in cases where we caught the disease a little bit too late and the tumors have replaced a lot of the liver, the liver is not able to sort of maintain its normal biologic functions, sometimes those are people that are high risk for treatment. And there is a group of patients with very large tumors that might at times display what we call arteriovenous shunting, where if we inject these microspheres they will flow through the tumor and up into the lungs. And this is something we need to be careful, to limit the dose to the lung because in some minor cases there can be some microspheres that distribute there based on normal flow and normal biology. So with experience we can pretty much select the ideal patients.

Andrew Schorr:

So Eva had this mapping that you did, and you said she was there four to six hours. So the idea is you're trying to look at exactly what her specific situation is, whether she's a candidate, and if she is then you plan your strategy, right?

Dr. Salem:

That is correct. The mapping angiogram, I'm doing nothing but thinking ahead. When I'm doing that mapping I'm thinking in four weeks, in eight weeks, in 12 weeks, in a year what am I going to need to do to target this entire area hopefully only once, but there are times when I need to go back in and repeat a treatment, so I need to be thinking well in advance of everything. So this is what the mapping angiogram does.

The other thing it does is it helps me identify small vessels that might be flowing outside the liver to, say, the stomach or the esophagus or other areas, and I want to make sure to try to avoid those vessels, sometimes even close those vessels to make sure that no spheres migrate as part of the normal flow in the liver to areas near the stomach, for example.

Microspheres**Andrew Schorr:**

Let's help people understand just what are these spheres. What do they look like? How big are they? What are they made of?

Dr. Salem:

So there are two types of microspheres. There are the SIR-Spheres and the TheraSpheres, and both of these use a similar concept. They are microscopic, micron sized particles, 30 microns to be exact, essentially the size or the width of a human hair, each one of these, if not less. And what we do is we inject millions of them, millions of these microspheres, and they because of normal flow will distribute into the tumor and lodge and sit inside the tumor and emit the radiation effect. Really what we're doing again is injecting millions of these microspheres because tumors in the liver cells have millions of small what we call arterioles, and so these microspheres will concentrate there, get blocked and get lodged there and emit that radiation.

Andrew Schorr:

It sounds incredible, I mean really. So these spheres go down the catheter to where you want them. Now, the big day came for Eva. And, Eva, first you had one lobe of the liver done in one session and then later a second lobe, right? All right.

So, Doctor, tell us about that, how you decide to proceed and why you would do one session and then another.

Dr. Salem:

So there are many schools of thought in terms of how to approach this. There are those that believe in doing lobar therapies, those that believe in doing whole liver therapies at the same time. And probably the data and the evidence has fluctuated back and forth in terms of whether you should do lobar or whole liver. Personally I've always done lobar treatments. I've almost never done whole liver at the same time. This is because when you do the entire liver it's potentially a bigger shock on the patient's system, although in some cases it certainly is very well tolerated. But for me it permits me to treat a portion of the liver, see how the patient will do.

And certainly in some cases the carcinoid crisis can be aggravated by treatment and so if you irradiate that entire field potentially that carcinoid crisis might be pretty bad and difficult on some patients. So I usually do one-half of the liver, usually the larger half, the half with most of the disease, and then I will see the patient at four or six weeks, see what we have done, see how things look, and then plan for treatment of the untreated side after that.

Andrew Schorr:

We should mention when you talk about carcinoid crisis, these carcinoid tumors, part of neuroendocrine tumors, actually have hormonal effects on the body, right, so they're not just physically blocking things?

Dr. Salem:

Yes. They put out hormones. That can become symptomatic, shortness of breath, diarrhea, abdominal pain, flushing.

Andrew Schorr:

Bad guys throughout the body, so you don't want that to happen. Now, Eva, so what was the post procedure effect for you? So you had the mapping and let's say after the first time what did you do when you went home or on the way home?

Eva:

Actually, on the way home I stopped at the grocery store and did my grocery shopping.

Andrew Schorr:

That's incredible.

Eva:

And I can only speak from my own experience, but I had no ill effects whatsoever.

Andrew Schorr:

Now, everybody's situation is different. First of all, who is a candidate for this, where their tumors are, how they're treated and certainly how they recover from the procedure. But, Doctor, we said that it's an outpatient procedure, so I take it that most people do pretty well.

Dr. Salem:

Yes. Most people do quite well, and if we weren't validating this over and over, this outpatient concept, probably would have stopped this years ago noticing that potentially patients were not doing very well. But this is again a thousand patients later now. This is consistent. Patients do fine. They can go home on the same day.

The biggest side effect, I'm thrilled that Eva had no side effects, but the biggest side effects in general tend to be fatigue. Radiation itself, no matter where it is administered, in the liver or elsewhere, can cause fatigue, and most patients that receive this therapy will complain of some level of fatigue. Now, it's very hard to attribute that fatigue to the treatment because these patients are sick. They have some level of fatigue already. Is it sort of the mechanics of coming to the hospital early, long day? Is the fatigue related to that? Is it fatigue related to radiation? It's difficult to tell, but certainly in my opinion there appears to be some level of fatigue that is caused by the radiation effect.

Andrew Schorr:

We have a lot more questions but the one question I want to ask Eva right now, Eva, how do you feel now? We're, what, about over a year after these procedures, 18 months. How do you feel? Are you working? How is your life going?

Eva:

I feel great. I'm really lucky that I have Dr. Salem available to me because I think having the right physician perform the right procedure is key to success. I working full-time. I have three adorable grandchildren that I spend every moment with that I can. And again I continue to feel really terrific. Despite carcinoid, which patients do have, as Dr. Salem spoke about, flushing, diarrhea, abdominal discomfort, I really don't have any of those symptoms. So I'm feeling terrific.

Andrew Schorr:

And a lot to live for. A lot to live for. We'll talk more about that as we go forward.

We're going to take a brief break and when we come back we'll have a lot more questions for Eva, about her life, and what she would say to other patients, but certainly for Dr. Salem and sort of getting more of the specifics, what conditions does this apply to, how is it evaluated and also about his level of experience with this and where this is going and is it just later stage treatment or can it be earlier. Much more to come as we continue our Patient Power discussion on neuroendocrine tumors such as carcinoid using radiation microspheres. We'll be right back.

Andrew Schorr:

Back with Patient Power as we continue our discussion with Dr. Riad Salem. Dr. Salem is the director of interventional oncology at the Robert H. Lurie Comprehensive Cancer Center at Northwestern Memorial Hospital. He's an interventional radiologist. And also with us is his patient who is doing quite well

even though she's had carcinoid tumors and many in her liver. She's been treated with the microsphere approach. Eva Donaghue from Arlington Heights and doing well.

So, Dr. Salem, let's continue. So carcinoid tumor, rare. Liver cancer rare too, but somebody, and I've had family members with it, they wonder, and the people will go as you know anywhere in the country, does it apply to other cancers of the liver beyond carcinoid that show up there?

Dr. Salem:

Yes. In fact most of the research that is done with this treatment and most of the people that are candidates for this are those patients that have what we call hepatocellular carcinoma, primary liver cancer, and metastatic disease of the liver of which neuroendocrine is one of them. The other one would be colorectal metastases, and this is certainly between those three probably the most common indications or reasons for using these therapies in these patients. We certainly have treated many of these patients, and again from a statistical standpoint colon cancer with metastases to the liver, neuroendocrine and primary liver tumor with HCC, hepatocellular carcinoma, are probably the most common reasons we would use this therapy.

Andrew Schorr:

Let's talk about metastatic colon cancer for a second. That is what caused the demise of my mother about 25 years ago. And so when it was discovered it had spread, and I remember the oncologist said, well, about 10 percent of your liver is now affected. And she had chemotherapy and the side effects of that, and she lived what at that time was seen to be a long time, about four and a half years, but certainly she went downhill. At that time I remember they were thinking, well, was there a drug therapy with a little pump that could go right to the liver, and I know she was not a candidate for that. It had something to do with the way her arteries were supplying the liver.

With someone like that, where it had spread to the liver but it's not the whole liver, maybe 10 percent, would it be any different now? I know it's tough to look at her case, but those kinds of cases where it has spread, where does this microsphere approach come in?

Dr. Salem:

So it is difficult without knowing many more of the details, but essentially there clearly is a role. In metastatic colorectal cancer the standard of care therapy that we have now are certainly systemic agents. If you are not a surgical candidate where you can cut out liver metastases then the next best thing is systemic chemotherapy. And we know that, and there is a rich level of data and evidence on this. The time when we consider this kind of therapy is when patients usually have failed first- and second-line chemotherapy because after that is where the difficulties come in, and the partial response rates start to decline significantly from chemotherapy. So are there patients who progress or don't respond to first- or

second-line treatment that have liver-only disease, they exist, or liver dominant disease where targeting the liver makes sense with this therapy, and certainly there are, and those are the patients in general that might be candidates for this treatment.

Patients that have metastatic disease to the lung, lymph nodes, outside the liver as well as the liver probably do not benefit from this kind of therapy to the liver because of the significant disease outside. But if you have liver dominant or liver only disease then there certainly is a rationale to target locally the liver disease in again the optimal patient and the proper timing with chemotherapy.

Treatment Approaches

Andrew Schorr:

All right. Let's talk about targeting the liver. So you've had external beam radiation, various chemotherapy, even chemotherapy delivered through pumps, as I talked about, to the liver, and then you have various ways of winding either chemotherapy or radiation right up interventionally. So how do you decide which approach and when?

Dr. Salem:

You mean comparing chemotherapy to the targeted liver therapy?

Andrew Schorr:

Yeah. Take us through kind of the range. For instance, there's systemic chemotherapy, but I mean if cancer is seen just in the liver and you have systemic chemotherapy you also have ways of delivering chemotherapy right into the liver. And then you talked about you have external radiation aimed at the liver, but then you have interventional radiation. How do you decide which to do when?

Dr. Salem:

So I think one always has to recognize what is the level of evidence with all of these therapies. What do we know? Are these based on small studies? Are they randomized studies? Is there really sort of acceptance among experts on this kind of approach? So certainly if patients are surgical candidates, resection of the liver metastases, that is one of the gold standards for metastatic colorectal cancer. The other gold standard is systemic chemotherapy if you are not a candidate. That is pretty universally accepted.

If you have never been exposed to chemotherapy and have liver metastases it's probably not the best approach to go with targeted liver therapy because there is a biologic process that is going on that without systemic control you may just be targeting the liver but yet any cells outside the liver you are not hitting or targeting with chemotherapy. And that's why usually what we want to do is have people get systemic chemotherapy, try to control the systemic disease, and if there's still persistent disease in the liver this is where we can augment the effect of chemotherapy by targeting the liver.

Andrew Schorr:

Now, targeting the liver. So I have actually been in the operating room and got to see a procedure. This was a number of years ago, radiofrequency ablation, where there was a doctor kind of physically zapping with radio frequency a little wand, I thought it was, but, at any rate, where the tumors were seen in the liver. That approach has been around a while. Where do microspheres come? Because I remember that had to be done in the operating room.

Dr. Salem:

Yes. So radiofrequency ablation (RFA) is in fact as you were describing it a small wand, a needle that is advanced into the tumor and where heat is created to ablate and burn that entire area of tumor and a small margin around it. Now, radiofrequency ablation can be performed in the operating room, in the interventional radiology suite. It really depends on the hospital, it depends on the local expertise, and it depends on the location of the tumor. The majority of the ablations here at Northwestern are done by interventional radiology. We have a very busy program that works on ablation, but certainly there are many cases that are also done laparoscopically in the operating room with the surgeon. So there are various ways of doing it.

But the indications for RFA are a little bit more strict. Smaller tumors, limited disease. So if you have multiple tumors, anything more than four, really RFA is probably not the best way to hit it because if you think about having four small tumors probably there is one or two little ones statistically also there that you are not able to identify, and so that's why the transarterial approach would target that entire area, and I think this is what we did with Eva.

Andrew Schorr:

I heard a doctor say the other day there are no dumb questions, but I'll ask one maybe, but you've probably been asked it before. So you said when you put in the microspheres it affects the blood flow to the tumor. But it would seem like if you're putting, you said, millions of microspheres, even though they're so small, how does healthy tissue stay alive while you're killing the tumor?

Dr. Salem:

That's a very good question. We talked a little bit earlier on about the concept of hypervascularity, which means blood flow that is preferentially going to the tumor as opposed to the normal parenchyma. So let's take a simple example of a liver tumor and an artery where I inject the microspheres. So when a tumor is very vascular, because I'm injecting, say, one million microspheres, because the tumors are hypervascular, say, 900,000 microspheres will go to the tumor but only 100,000 remain to go to the normal liver. So it's a good question because there is some exposure of the normal liver to radiation, but we know that the liver can tolerate this normal exposure. So the more vascular a tumor physically the less the number of microspheres that are available to go to the normal parenchyma. It's a very simple process.

Andrew Schorr:

Are there two processes going on? One is these little beads or spheres are actually physically blocking blood flow to the tumor and then radiation kills the tumor, or is it simply delivering the radiation?

Dr. Salem:

That's a very good question and this is really an area of discussion and research when we compare the products of TheraSphere and SIR-Sphere. The TheraSphere product has a very low number of microspheres. This is what we used with Eva, and most likely there is very little if any blocking effect. Really it's working as a radiation delivery platform.

With the SIR-Spheres you're injecting a little bit more microspheres, and so most likely there's a combined radiation and embolization effect. We don't know where the optimal area is, and we're researching this, in fact, at our institution, but there probably is a combination of effect. With SIR-Spheres, although it's very hard to demonstrate this conclusively, but again there is a spectrum of radiation to embolization and that's why this therapy is also called radioembolization.

Andrew Schorr:

Now, I know another hot topic at your conferences is how early do you use this. So if you have the situation where somebody has many tumors, like Eva did, spread throughout an otherwise healthy liver, then do you wait to use it? It was used pretty early with her. I mean she had been living for a couple years with all this whole journey she was on, but still she didn't have any other kind of surgery other than the removal of a blockage. So how do you decide whether it's third line, second line, where it fits in?

Dr. Salem:

That's an excellent question. Patients with neuroendocrine tumors really tend to have very slowly progressive disease. People can live for 10, 15, 25 years without any need for intervention in the liver or elsewhere. Sandostatin is one of the gold standards for this kind of therapy, but when you think about when to use it, in my experience most patients undergo treatment or at least stabilization treatment with Sandostatin.

And what happens then is you then decide based on how patients do on that therapy whether they should be treated to the liver. And since most people are stable what we usually do is observe the tumors. If there's any sign that they are getting slightly larger, and if I remember correctly with Eva, that was the case. They were getting very slightly larger, very slowly, but they were enlarging on Sandostatin. That's when we decide to target the liver.

The other time when we might use the therapy very early on, before we document progression, is when the tumors are very large or very symptomatic patients because larger tumors are difficult to shrink than smaller tumors. So we don't want to wait for a large tumor to become even larger which will translate usually into a

lowered response rate for our ability to shrink the tumor. So in these cases usually these are times when we might treat people a little earlier, but otherwise in general we usually wait until there is some type of progression on Sandostatin because that can take a long time and we try to spare patients unnecessary procedures.

Listener Questions

Andrew Schorr:

Okay. So you talked about sometimes patients needing to go back. So Matt sent in an e-mail question from Chicago, and he says, Doctor, "How many times can I be treated with microspheres, and why would multiple treatments be necessary?"

Dr. Salem:

So radiation therapy is one that is usually applied at scheduled staged intervals. If you think about radiation therapy to the prostate this tends to be a four- to six-week process where patients come in every day for radiation. The microspheres are a little bit different, and we continue to learn from this. We are now applying this one time. We apply it one time to see how the tumors respond, but if you think about other radiation therapies nobody applies radiation one time. You usually do it several times. But the radiation dose here is so high that we believe that potentially it offsets the need for multiple treatments.

To answer the question in general we have patients that have received multiple treatments, and those patients are the ones that have persistent blood flows to those tumors, and as long as there's hypervascularity, blood flow to those tumors, we can repeat treatment. Once the hypervascularity disappears this is when we try to think about holding off treatment because now there will be exposure of normal liver tissue to the radiation.

Andrew Schorr:

I've got another question for you. I guess I have the benefit of having done a lot of programs and some were with your transplant colleagues at Northwestern, and I learned about the liver, how it regenerates and how liver transplants are done. And Eva, you wondered too, right? Could you have a liver transplant some day, right?

Eva:

I did originally wonder that, yes.

Andrew Schorr:

Okay. Dr. Salem, help us understand in this setting people must ask you, well, couldn't you just give me another liver or I understand a liver can regenerate, just take away the bad part and leave the good part and it will grow back?

Dr. Salem:

Liver transplantation in the context of neuroendocrine is controversial. I believe one of the busiest programs in this is at Mayo Clinic in Rochester, but I would have to verify this. But it's not really one of the main accepted indications for

transplantation. That tends to be primary liver cancer, hepatocellular carcinoma, that are within a certain stage with small tumors. Those are patients that we think that have malignancies that we consider transplantation.

But in neuroendocrine it's still an area of research. There's no large, prospective randomized studies that discuss this to establish its role, but it certainly is something that is very interesting to the neuroendocrine patient population.

Andrew Schorr:

And we have a shortage of donor organs of course.

Dr. Salem:

Absolutely.

Andrew Schorr:

That's an overriding problem. All right. We talked about retreatment. We've got some other questions from our listeners. So we mention the liver. Erin from Chicago wondered beyond the liver are there other organs like the pancreas that could be treated this way? I've had a relative with pancreatic cancer so I'm sure they wonder.

Dr. Salem:

That is also another great question because the blood supply to the pancreas is in fact quite rich and theoretically we are able to get catheters into the pancreatic arteries. And in fact our group has published several papers talking about catheterizing the pancreatic arteries. The problem is the pancreas is a very sensitive organ. Somebody can receive a trauma to the abdomen, a punch for example, and can develop something like pancreatitis. And so it is very sensitive to radiation, and one of the things we don't know is how the pancreas would respond to very high-dose radiation. The liver we know can tolerate high-dose radiation without any significant inflammation, but if we treat a pancreas tumor where we could kill the tumor but develop major pancreatitis, this is certainly something that is concerning because depending on severity that can be life-threatening.

So we can catheterize the vessels, but there's very little research done on this. As you know, pancreatic cancer is relatively rare compared to others and there's very little research done on this to begin with let alone catheterizing the artery and let alone injecting radiation microspheres.

Andrew Schorr:

Dr. Salem, just so we're clear with everyone. For these microspheres what is their approved use right now?

Dr. Salem:

There are two devices, as I mentioned before, TheraSpheres and SIR-Spheres. The approved indication for TheraSphere is primary liver cancer, hepatocellular carcinoma. The approved indication for SIR-Sphere is metastatic colorectal cancer.

Andrew Schorr:

All right. But you were able to use it experimentally with Eva with carcinoid tumors. Now, Eva, you had a big battle with your insurance company, right?

Eva:

I did.

Andrew Schorr:

I mean an appeal, and how thick were those documents you sent off?

Eva:

About six inches.

Andrew Schorr:

Oh, my. So, Doctor, you have to go to bat and the patient has to go to bat, but is it your experience that the evidence is mounting that it can be helpful, as it's been in this case.

Dr. Salem:

Boy, this is a--

Andrew Schorr:

A sticky wicket. And with healthcare reform too.

Dr. Salem:

With healthcare reform this is a difficult subject to address. First of all, indeed, these are uses of these microspheres that are not in their primary indication, but we must recognize that in medicine it is impossible to have all medications, all devices approved for every possible circumstance, scenario and disease state. This would be impossible to do, as you might imagine, so we have to have the flexibility in medicine to use one therapy that might be approved for one context that we believe might benefit the patient. And that's in fact what happened with Eva.

And, yes, we filed a lot of paperwork and the letters of necessity that I had to write and Dr. Benson, we did a lot of work for this. And that is just a reality of the system that we are dealing with. So that really sort of sets what is the background that we have to deal with this kind of insurance context. I don't know that I would label this as experimental when we use these devices as what we call off label, but certainly when there is plenty of evidence to use it we have to make medical decisions to consider that.

The other thing is one of the things we follow or the guidelines we follow are the NCCN guidelines. And if you look at the NCCN guidelines the panel of experts have added radiation microspheres as one of several options for patients with neuroendocrine tumors.

Andrew Schorr:

All right. That's very helpful. We have more questions coming in, more to talk about as we continue our discussion with Dr. Riad Salem and Eva Donaghue, his patient, and help understand where this targeted therapy comes in and also how it affects your options going forward. All that coming up as we continue Patient Power right after this.

Welcome back to Patient Power as we continue a fascinating program, and it's really thrilling to me when you talk about new medical technology that's really making a difference. You know, there's some that are not breakthroughs, but some are, and imagine these little, tiny little spheres that can go up from the groin, get to where you need to go, in this case the liver, and starve off the blood supply to those tumors that are in the liver that otherwise could cause big problems. And that's what we're talking about with Dr. Riad Salem, who is an interventional radiologist, and he's the director of interventional oncology at Northwestern's Robert H. Lurie Comprehensive Cancer Center in Chicago. And Eva Donaghue, 60 years old, looking forward to celebrating Thanksgiving with all those great grandchildren and children and feeling great after having this procedure with Dr. Salem.

So, Doctor, one of the things you wonder about is, and I'm a cancer survivor, leukemia survivor, and we learn certainly with systemic therapy that sometimes you have a certain drug or combination of drugs and that hopefully does its job against the cancer but it kind of closes off some options down the road. With these spheres close off other options?

Dr. Salem:

So again as we think about new therapies that we develop for some of these patients we have to be thinking ahead, and that's a very good question because this is really one of the advantages of this therapy is that because you are not permanently blocking the blood flow to the tumors but rather delivering this radiation therapy, the vessels stay open. So if for some reason the patient does not respond to this therapy then the vessels are still open and you can go back in there and inject something else. Maybe these tumors won't respond to radiation but will respond to chemotherapy or to other types of therapeutics that we would inject through the artery. So that's one of the advantages of this, is that the vessels are patent, they stay open, and we can treat with something else should the patient not respond to this.

Andrew Schorr:

We had a question come in from Dave in Chicago. I'm not sure exactly what this means so you can help us. He said, "What is RAD001? He said, "I've heard it can be effective in treating neuroendocrine tumors. Can you tell me more?"

Dr. Salem:

Boy, I think RAD001 is everolimus, which is an mTOR inhibitor, and this is a new drug or a new device--I'm sorry, a new drug that is being tested in patients with

neuroendocrine tumors. So I believe this is an investigational drug that is being studied right now. I don't know the specifics of any of the outcomes recently, but I know it is being studied. I believe again it's an mTOR inhibitor and one of several drug options for patients with neuroendocrine tumors or at least being considered for neuroendocrine tumors.

Andrew Schorr:

And just so I understand because people hear terms and they don't know what it means. I know with TheraSpheres the radiation side is called Yttrium-90, think. I don't know if it's different for the SIR-Spheres.

Dr. Salem:

No, they're the same. They're both Yttrium-90.

Andrew Schorr:

And so these spheres go in but they don't come out, right? So you have this radiation that goes in. What is the, I guess you'd call it the half-life? I mean, do I have to worry about all these sort of spheres inside for the rest of my life?

Dr. Salem:

Yes. The microspheres do stay lodged permanently, but the half-life is about two and a half days. So if you think about physics and decay, usually by about ten days, two weeks or so, most of the radiation is gone. But these microscopic particles, yes, they do stay inside the body forever. But this is analogous to surgical clips, for example, when you have an operation. These are benign sort of remnants of the therapy that do stay lodged permanently, yes.

Andrew Schorr:

So there's Eva with her grandchildren, so because you've been radiated, if you will, you have radiation inside you, does she have to stay away from her grandchildren if it was right after the procedure? Or what precautions are there, if any?

Dr. Salem:

So there are no clear guidelines on this, but just some recommendations. At our center we recommend people stay away from close and prolonged contact with people for the first three to five days. This radiation is what we call beta-emitting radiation which means that most of the energy is absorbed very locally and very little of the energy is emitted outside the body. But despite this there can be some radiation that is detected, and we try to take a very conservative approach to that, and that's why we tell people to just stay away just for a few days. And people just adjust their life for a few days from a close contact standpoint. And I mean very close, not in the same room or anything like that, but very close contact for a few days.

But otherwise there are no other precautions. As you heard, Eva went to the grocery store right after the procedure, so there are no major public safety issues here. This is very low dose radiation when you look at what is emitted externally.

A Major Advance: What the Future Holds

Andrew Schorr:

Dr. Salem, for me, just a member of the public, when I hear about this it just sounds like incredible technology that allows you to do things that really can make a difference in a much less invasive way. Am I making too big a deal of it? I know doctors like to be conservative and certainly in an academic medical center such as yours not to say this is the greatest thing since sliced bread, but it seems like it is a true advance.

Dr. Salem:

It is a major advance. We have to be very cautious in how we state things and how we position things. This is, I believe, an advancement in how we treat liver tumors. Certainly neuroendocrine tumors in my experience have responded extremely well to this therapy, having treated again hundreds of patients with this condition. So it certainly is an advance.

And I think the sheer fact that we are able to target the liver with high doses of radiation with an outpatient therapy, to me the outpatient concept is extremely attractive. People really want to know about quality of life when you are undergoing any type of treatment, whether it is cancer or not cancer. And the fact that people come in, they get treated, and as in Eva's case go to the grocery store, that is a major advancement.

Andrew Schorr:

Now, Eva, as you have told people about this you've heard that this sort of procedure is not done at every hospital or by every doctor. So in your case you went to a major academic medical center. You had the benefit of Dr. Benson as well on the medical oncology side and a whole team. It sort of takes a team like that to really assess whether this is right and whether they can do it there, I would imagine.

Eva:

Oh, absolutely. And the patient has to know their body best. They know what their requirements from their physicians need to be, and I think the patient has to play a very, very important decision-making role in what happens to them.

Andrew Schorr:

Now, you networked with other patients related to carcinoid tumors, and that was a blessing for you, too.

Eva:

Oh, the Caring For Carcinoid Foundation has been a godsend. Susan Lumley who has a Y90 support group has been instrumental. Everybody in Dr. Salem's office is a whole team, and I think Dr. Salem would admit that the whole team of folks that he works with at the hospital really benefit the outcome.

Andrew Schorr:

That's what I was going to ask you about, Dr. Salem. It seems like it does take a team. So you are an interventional radiologist. I'm sure there are like nuclear medicine people around. You're delivering radiation. But just the whole work-up for patients it seems like it takes a very experienced group to then be able to do this time and time again.

Dr. Salem:

It does. And our group that we developed is focused on interventional radiology with nuclear medicine support in physics, and in some centers radiation oncology is involved. We have a very active program with our nurses. They are extremely involved in helping and assisting patients, as Eva knows, in terms of organizing, getting preauthorization, looking at follow-up and meetings discussions. All of this is something that we take very seriously because this is our job, our duty, to really facilitate things for patients. And, absolutely, I take tremendous pride in the team that we have built here at Northwestern.

Andrew Schorr:

Where are we headed with this? So you have been involved probably I'm sure in the investigation of these technologies, the microsphere technology. Where are we headed?

Dr. Salem:

There are a few areas that I think are particularly interesting. One of them is if you look at the radiation oncology paradigm, that is one paradigm of chemoradiation where you give somebody some chemotherapy as a radio sensitizer to improve effect of radiation. So now what we would like to do is to do the same thing with this therapy and talk about chemoradiation to liver tumors, really sort of a new concept. Hasn't been done that much before, and because we can give much higher doses of radiation we feel that this is a major advance or certainly something that we need to investigate.

The other area that is very interesting is to combine these with chemotherapies and other systemic agents. I told you before that people with liver only tumors are probably good candidates for this therapy, but what if you have just a little bit of disease outside of liver? Maybe it might make sense to treat that large liver tumor with this therapy but also provide systemic therapy to cover the other area of the body that cannot be covered by this therapy, sort of a combination type therapy. I think this is certainly two of the areas that are extremely interesting.

The other places that would be nice to do all those very difficult because of research funding and budgetary limitations is to explore this, as one of your audience asked about, where can you use this elsewhere. I would be interested in doing some work on renal tumors with this because they too are very vascular. Some brain tumors are very vascular. Potentially they might benefit from this. But the research environment for this sort of thing is extremely difficult.

Andrew Schorr:

Eva, so we have people listening maybe around the world and maybe diagnosed with one of these rare cancers, like you were, carcinoid, neuroendocrine tumors, but whether it's that or liver cancer or it's colon cancer that's spread to the liver, what would you say to them so that they don't sort of give up and so they really seek out a center such as experts like Dr. Salem where they maybe have options that they're not hearing about somewhere else?

Eva:

Well, the best advice I can say is arm yourself with the right arsenal. Be your own advocate. Keep pushing for the answers that you believe are right. Find the right doctors for you. Get the right treatment at the right time. Know all the options, the risks and the benefits. And you have to really play an active role with your physician team to make sure that you're making the best possible decision for you.

Support groups are critically important. You have to remember when you go to those support groups there is a lot of information out there, and you have to spend some time investigating the facts. But you really have to continue to push, as we did, for this treatment which now 18 months later continues to benefit me.

Andrew Schorr:

Eva, one last question for you. If you don't mind, I'll just share. It's been a rough year. Your husband, John, died suddenly of a heart attack, and you'd been married almost 40 years, but now we're, almost, as we're recording this at Thanksgiving time and you're going to be with children and grandchildren, and your health is good and you have the opportunity to speak to so many other people and offer inspiration and hope. How do you feel about the future?

Eva:

Oh, I feel like there is hope. I know at one time I was told I might have two to three years to live, and I said to one of the physicians who told me that that I think you forgot that it's 20 to 30 years to live. Live every day to the fullest and continue to fight for what is right. Enjoy every single moment. The good things, don't focus just on the illness, which can become a very important part of your life, but there are so many other aspects to your life that are the best medicine as well.

Andrew Schorr:

Well, you do great work, I know, and you're running a volunteer program at the blood center, right?

Eva:

Yes. Thank you.

Andrew Schorr:

That's great work. And then you've got those three grandchildren.

Eva:

Yes.

Andrew Schorr:

So I hope you enjoy them. Is there anything you want to say publicly to Dr. Salem and his team?

Eva:

Yes, I wish there were enough words, I had the right words. I've had this opportunity before and I never say the right thing, but I feel that we put a lot of pressure and a lot of responsibility naturally on our physicians, and we call them heroes and miracle workers, and our expectations are so high, but his team and he have such expertise, such skill, such not only technical skill but the skill to listen to a patient and such energy that I want to thank him for giving me my life because I don't know where I would be today without him.

Andrew Schorr:

And, Eva, not only do you feel great but your tumors have been shrinking, so it appears that the technology that was brought to bear and the skill with the microspheres certainly has been doing its job in reducing the size of those carcinoid tumors. So great news. Makes it worthwhile, doesn't it, Dr. Salem?

Dr. Salem:

Absolutely. You know, I've been a practicing interventional radiologist for 15 years now and this is why we do this, is for patients like Eva and others where we can really make a big difference. And really I've known Eva now for two and a half years or so, and you know it's been a pleasure and certainly it's always an honor to speak to her and see her. And we're always thrilled to see how well she's doing because as you were alluding to before this makes a big difference for some patients and Eva certainly is one of those patients. And we certainly look forward to seeing her certainly for years and years to come and to interact with her and see her have many more Thanksgivings with everyone. It's always a pleasure to see Eva in my clinic. In fact, I saw her, as you know, a few days ago and these really for me are social visits. They're not just medical visits, they're social visits to see how she is, how she's doing, and it really is always a pleasure.

Andrew Schorr:

Well, it makes medicine worthwhile and the technologies and the targeted approaches that you're able to be so skilled at, thank you for what you do, Dr. Riad Salem, director of interventional radiology at Northwestern's Robert H. Lurie Comprehensive Cancer Center. Thank you so much for being with us, Doctor.

Dr. Salem:

Thank you.

Andrew Schorr:

And Eva, all the best.

Eva:

Thank you.

Andrew Schorr:

Have a great Thanksgiving. I always like to tell people when there are little kids involved, and I'm a cancer survivor too, I want you to dance at their weddings, okay?

Eva:

Exactly. I hope to do that.

Andrew Schorr:

Okay. Thank you so much. This is what we do on Patient Power. I'm so grateful to Northwestern Memorial Hospital. We're on our third or maybe going into our fourth year of doing these programs. There's a vast library on the ihealth area of nmh.org, and then of course these programs go far and wide around the world hopefully to make a difference and hopefully we did that for you today.

I'm Andrew Schorr. Remember, knowledge can be the best medicine of all.

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