STACEY QUINTERO WOLFE, MD: Thank you all very much for having me. Let's see. Is this our clicker here? All right. So I'm going to come and just talk to you a little bit about my experience with endovascular treatment for a wide variety of diseases. Obviously we're not going to cover every aspect of cerebrovascular disease.

While I could talk forever, you would clearly be bored to tears. I'm going to try to hit the highlights, hopefully keep you awake, because I know you guys have been at it all day long here and any questions-- this will be informal so anybody has a question, throw up your hand, and we'll see if we can get them answered. But this is-- just like I said --a brief overview of things that we can do endovascularly.

Obviously, for a long time we've been taking care of aneurysms by clipping them, and it's a nice adjunct to be able to have some patients that we can take care of without cutting their heads open. If you tell somebody, I could cut your head open or I could make a small incision in your groin, that's a little dicey as well. I usually tell them it's an IV stick. That's much better. But they like that. That's certainly good for patients now. That doesn't mean it's any less of a surgery.

We can cause a lot of problems, obviously, this way. It's not non-risky, but the recovery time is very fast. And so it's really nice to see these patients the day after surgery drinking their coffee and reading the newspaper in the ICU saying, when can I go home, Doc.

And that's definitely a different view than we get of patients that have to have a clipping. Just going over aneurysms, the prevalence-- it's there. It's not commonplace, but it's something that we certainly see every day where we are right now. Some of them rupture. Some of them don't.

The ones that do rupture are very dangerous, as you guys all know. You're looking at-- about a third of them die before they reach the hospital. A third of them will recover, but not fully. They're not themselves anymore. They're not holding down a job. And then a third of the people are, thankfully, able to make a good recovery.

This is a very busy slide that you don't have to know all of the details of. But when I talk to my patients the big question is, I have an aneurysm. Does it need to be treated or not? That's the most important question. What is the risk/benefit ratio of should we treat, should we not? So we started learning what the real data was with ISUIA in 2003-- the prospective arm of that-- and so all of this data and what have you-- these are the five-year averages of rupture rates. What we found out is that they didn't rupture as much as we thought.

That made us a little bit more conservative about what we were taking care of, and it definitely gave us some numbers to start with. And those have actually just been confirmed with the Japanese registry, where they followed 5,000 patients. This was 2,000 patients. And so we know that anterior circulation aneurysms, excluding PCOMs-- we group those into posterior circulation aneurysms because that's what they act like. They don't rupture nearly as much as we thought. This also gave us that number-- the magical number seven.

What I tell my patients is, as that aneurysm is growing, that thin wall is stretching. The more it grows, the thinner that wall gets, the more likely it is to rupture. And that certainly makes sense to them.

Seven seems to be that magical number where you go from a small rupture rate-- so basically looking at aneurysms that are less than seven millimeters --you're looking at roughly 0.5% per year. As soon as they get over that seven millimeter mark, then you're looking at much higher, somewhere between one to three depending on their morphology, the size, et cetera. When you start jumping up and getting into the 12 millimeter, 13 millimeter, that again jumps to where you're looking at 3% to 5% per year, and so that continues to increase.

Now, that said, we know that aneurysms that are two millimeters and three millimeters certainly can rupture, and the ones that are scariest to us are ACOM aneurysms, PCOM aneurysms, and aneurysms that have daughter sacs on them. Again, this makes sense. If you have a thin wall and you stretch out a thinner bleb on top of that thin wall, it's really, really thin, and they will rupture. And so the ones that look like bow ties, or little wind socks, or funny dog bones, those are the scary ones. And those we would say, we need to treat those sooner.

So ignore all of this busyness. Suffice it to say if it's less than seven millimeters for the most part we can watch that, unless we see that it's growing or it's really funny-shaped. If it's seven millimeters or greater, for the most part those need to be treated. So, like we talked about, clipping-- that's the age old treatment, and for some aneurysms is still absolutely the right choice for them.

Endovascular coiling and/or remodeling because we don't just coil anymore. We coil and we stent and we balloon-remodel things and now we have the Pipeline. So I'll just go through some of what that entails and then, of course, observation for those small aneurysms. Again, when you're talking about less than a 1% chance of rupture, I tell my patients that means 99.9% chance or 0.5% chance you're not going to rupture. So that's definitely the right treatment for some folks.

Location of aneurysms, ACOM, PCOM, and posterior circulation, the basilar PICA aneurysms. Those are the most dangerous. The morphology in this aneurysm that you see up here was a lady that I treated. I was following her for a-- where is it. Right there. --a 3-mm PCOM aneurysm. I did her 6-month interval followup. The first followup I do closely and it was four millimeters.

So I said, you know what, let me follow this a little more closely. So I did a 3-month one, and it was five millimeters. Every time it developed another little daughter lobe here, and so we went ahead and coiled this off and took care of her. But when you see that happen, it's time to take care of them.

The other thing that we have to look for is the availability of surgeons, resources, what is the natural history, do they have a family history of it. That's certainly a question we get very often. My mom had one. What does that mean? For the most part, aneurysms are not genetically passed down. However, we know that if you have two first-degree relatives-- so this doesn't mean the second cousin twice removed kind of thing. This is two first-degree relatives with an aneurysm, a cerebral aneurysm. You have about a 10% chance. So, again, not very high, but that's something that you can reassure patients with a little bit if they have a distant cousin that had an aneurysm. No, they're probably not at any higher risk for a rupture or for having an aneurysm.

With the coiling, what exactly does this mean? We go ahead and we put a tiny little catheter. It's about the size of a piece of uncooked spaghetti, but very pliable, obviously. We put that up into the aneurysm over a very soft wire. Through that we put these titanium coils, and they come out even if you deploy them outside of an aneurysm. They come out looking like this ball of yarn. They have a 3D shape to them. And we fill up the aneurysm.

The purpose of this is basically to occlude the space so there's no space for blood to go and to form a surface here so that now the vessel can endothelialize from both sides-- grow a new vessel wall across that aneurysmal neck. If you have an aneurysm that looks like this, those are beautiful because there's a lovely neck. Look at that. Ball of yarn stays in there-- no problem. But they don't all look like that, unfortunately.

We'll get to, then, what do you do when it doesn't look like this? Obviously, you can imagine if this coil bunch falls out, that's a huge stroke for the patient and a major problem. This is an ACOM aneurysm that I did just after I got here. And so you can see, this one actually had a little daughter sac on the other side of it, but we were able to put in here. So the first coil you can still see that there's filling because we only have a small amount of it filled up. And then this is after three coils. This was a 4-mm ACOM aneurysm.

All right. Sorry. We cut off the top there. Balloon remodeling. So what happens when your neck is a little bit too big, but you still think if you can get this to take a shape, you can get it to stay in the aneurysm. If you can get a couple of them tangled up in there, they won't come out. And so this is basically a balloon blown up here. You can see over the wire and that's just making sure that this is not prolapsing into the parent vessel. Once you get them all tangled up, you can see-- here is our aneurysm. Now it's gone. You see a little bit of the PCOM actually filling behind that.

Sometimes they're crazy and big. Now what can you do? You can do all kinds of iterations with balloons. You can see how we put a balloon up into each PCA here, blew those up, and then that's how we got our coil to stay. This was before stenting became very commonplace. Now I would probably have a stent at least into one of these to help again create a scaffold for the endothelial cells to grow across.

This is a stent here and you can see how it flares out so that it grabs the wall of the vessel. You can see these are markers so that we can actually see it in the patient and know where it goes. And we can put our catheter either through or just behind the stent, put in your coils, and then that's going to keep it there.

Now of course the problem with putting a stent in is that, that patient is forever going to need to be on aspirin, so usually six weeks of Plavix and aspirin and then at least 81 milligrams of aspirin lifelong. You guys might have heard of Pipeline. This is one of our newest things to come along and change the way that we look at aneurysms.

When you have big, crazy aneurysms that are 360 degrees around the vessel, what can you do for that? It's difficult to clip that. At best, you could clip both sides, but you're still going to have aneurysmal wall there. A stent, if it's sturdy enough potentially, but then you have to somehow coil 360 degrees around it, and, if you can imagine, as you start coiling around it, you're blocking your view. You're filling it up with metal. You can't see through that. So there's a lot of problems with that type of an aneurysm.

We came up with Pipeline. This is a stent that just has a whole lot of metal to it. OK. Instead of having those big spaces that you can go between, much less space in between the interstices of the stent. It gives you this high coverage, but at the same time you can still get some blood through.

So if there's a sump, if there's a vessel that's requiring blood flow, that vessel will stay open. This is a pseudoaneurysm that I did, but this also works for anterior circulation giant kind of aneurysm. Oops. Sorry. All right. Basically here you can actually see the stent. This is the wire that it's on-- this dark thing --and then here's the stent just starting to deploy. It looks a little bit like a trumpet. The stent goes from here to here.

This right here is the carotid artery coming up. You've got your ACA, your MCA, and this right here is a dissection with a pseudoaneurysm. This is a 21-year-old guy, healthy guy in the Army National Guard, minding his own business and having a good time on a Friday night and gets a bad headache. And, sure enough, he's got subarachnoid hemorrhage, and what do you do here? Now the alternatives are that you can go-- you clip here, click there, clip there, OK, lose a couple of lenticulostriate perforators and then bypass that to keep it from rupturing again.

We know that dissections are very, very dangerous. You have about a 25% chance of re-rupture in the first week to two weeks, and a lot of those patients don't make it. So you do that. You give him a stroke, knowingly, to save his life. From 21, that's not really what I want having to have happen in my head.

We were able to put up this Pipeline stent here. This is looking at it end on. It's here in the MCA and you can actually see how thick that stent is, and then here's a 3D reconstruction afterwards. So we see the ACA coming in. You've got a little flow artifact so it looks a little thin, but it's filling well, and you can still see there's a little blood getting through. This is not normal. But now after six weeks and then three months, he is revascularizing this wall and taking care of this aneurysm without a stroke. This just gives us one more tool to do stuff that we just couldn't do before.

Vasospasm, another thing obviously. This is going to happen with the patients that actually rupture. I'm not going to kill you going through vasospasm, but initially our treatment was hope for the best, give them some fluids, give them a higher pressure, and hemodilution. We would bleed the patients. Very bizarre stuff. We got a little better with calcium channel blockers, some data with magnesium, and that's a little bit up for grabs. The same thing with statins. All of those things help, but angioplasty is definitely a definitive fix.

You can see this patient is postbleed day seven. She's got here a little bit of spasm in the ACA. You can see some distal spasm here. And then look at her MCA. This is the M2 so her M1 should be at least this size, if not twice the size of this. We were able to go up with the balloon and you can just see the difference that something like that makes.

So moving on again, this is a grab bag of all fun things that we can do. AVMs are less common than aneurysms, certainly. We think that they are congenitally-based lesions, but you're looking at a rupture rate of about 3% per year. OK. Again, not horribly high, but when you look at somebody's lifetime risk-- the easiest way to do lifetime risk is 105 or if you can't remember that --just 100 minus their age. And that gives you roughly their lifetime risk of what their hemorrhage would be. If you've got a young patient, that's fairly high and so that's the reason to treat these.

Now some of you may have heard of the ARUBA Study. Does that ring any bells? The ARUBA Study is a study looking at, do we treat these AVMs? Do we not? The findings of the ARUBA Study was actually there's higher risk involved in treating them than just leaving them alone. It's a randomized, controlled study. You never want to discount that. The only problem with this is that they're looking at three years.

So of course you're going to find that. You're taking all the risk upfront and you've only got three years of a rupture risk of 3% per year. Before we stop treating AVMs altogether, I think that we need to continue looking forward with that, but certainly good to know about and patients may ask about that.

We have to really think about what it is that we're doing. If there is an intranidal aneurysm, a flow-related aneurysm, or a venous outlet stenosis-- remember you've got arterialized blood coming in, and it's coming into the venous system directly. The venous system is equipped to handle pressures of zero to five. Arterial blood is 120 or 180, depending on how well your patient's blood pressures are controlled. So if you have a venous outlet stenosis, much higher risk of rupture.

Surgery certainly for many of these is definitive and is very safe to do. You can do this with a risk of only about 1% to 2% depending, of course, on where it is. Embolization a good adjunct. Cure rates are very small. You have to have almost a single feeder in and single feeder out in order to cure that. And then radiosurgery.

Again, if you tell me, hey, I could cut your head open or I could just put a frame on there and zap you once with a laser. This is not a laser, but all the patients think that it's a laser, and that's very desirable and certainly the best treatment in many lesions, especially if it's an eloquent area and if it's a small, compact nidus. But we have to remember that only about 80% of these go on to actually occlude, and that happens somewhere at three years so you've got that lag time.

Certainly if you have any of those associated aneurysms or venous outlet stenoses, that could be a problem. The most recent studies just came out again from Pittsburgh looking at 2000 patients and finding about 8% to 10% of radiation necrosis. So it does come with risks.

Our newest revolution, I will say, in AVM embolization is Onyx. It's basically black glue. It used to be you had one shot of glue. You had about 30 seconds to get your catheter out before it glued itself in. Let me tell you. There's just nothing like gluing a catheter to get the heart rate going. With AVM embolization with Onyx, it doesn't attach itself to the catheter so you can have about 45 minutes, and you can really get quite a nice cast. You can see. Here is your AVM. This Is the MCA. You see how this is fairly enlarged. It's almost the same size as the distal ICA.

AVM nidus. Here's your early venous drainage. Got a big venous aneurysm on this guy. Basically you put your catheter way out here and then you start, and this is what it looks like on subtracted angiogram. This is what it looks like just on plain x-ray, but, you can see, here's your feeder, and you really got the Onyx all throughout the AVM. This make surgery a lot easier. Now you've turned it into a tumor instead of many bleeding blood vessels. That's nice to be able to do. Embolizing it in order to make it smaller for Gamma Knife or radiosurgery-- a little bit difficult.

We're finding that if you don't radiate it, it doesn't go away completely. They have a life of their own. They will start growing. They will develop more nidus, more feeders, more venous drainage, and so this alone would not cure this. Even though it looks good right now, if you look again in six months it's back and usually with a vengeance. It starts growing things.

All right. Stroke. This is what I was originally supposed to talk about. We all know stroke is pervasive and it's problematic. It's devastating to the patient, to the family, in health care dollars. It's certainly a big problem. As far as what we do and why we can do it, it's stroke versus penumbra. What tissue is dead? What tissue is there to save? Most tissue doesn't die for the first three hours or so.

However, there's a large variation. It depends on where the stroke is, how good the collateral circulation is, how hot or cold the patient is. A lot of these things all play together and so when you look at the animal studies, that's where we came up with this three hours. And then of course we started looking at stroke and giving t-PA and trying out different stuff, and we knew that somewhere between three and six hours is the time where you can save some people. Other people you can't save.

In this-- this is basically your diffusion MRI, so you're looking for a restricted diffusion or white spot on that. That's dead tissue. It is not going to come back. On the ADC map that should match up as being dark, OK. Now when you do a perfusion, this is all the area that's not getting blood flow-- not dead yet --but not getting blood flow. And so these are the patients that we're after to see-- can we help them out. If the tissue is already dead, we know that we can't help.

tPA. You all know about tPA. This is where we started with the NINDS Trial. What I always like to go back to thinking about here is that 20% of patients will have good outcomes. OK. Modified Rankin score 1 and 2 Doing nothing. They get better from their stroke, about 20% of people.

So IV tPA is certainly our gold standard, but we only make with that about 31% of people back to good outcomes. So we really have a ways to go. There are still 70% of people that are not doing well. Now some of that is logistics, getting to the hospital fast enough, making sure we can get them through their workup and to the tPA. There's a lot of stuff that goes into that, but we certainly have a lot of room to work.

ECAS brought us out to about 4.5 or 4 and 1/2 half hours. This is not for everyone. These are more selected patients. We know that older patients-- greater than 80 with a lot of atrophy --these patients don't do as well the longer you wait. And it's because they don't have that collateral circulation anymore. And so those patients-- you revascularize them. You can get rid of the clot. The question is, should you?

Because if you get rid of the clot and you have dead tissue, that's what you're potentially going to bleed into. We look at these patients, but a lot of patients we can still treat with IV tPA up to 4 and 1/2 hours.

Contraindications. You know so many of these. Obviously hemorrhage, if they have had recent surgery or if they have had a recent car accident, trauma, seizure, something like that. If they have rapidly improving symptoms. So if you have somebody who's improving in front of you, don't give them tPA because then we've given them the risk without the benefit. They are in that 20% that's going to get better by themselves potentially. If you have elevated INR or PTT, somebody on Coumadin, but who's subtherapeutic. So they get a stroke from their AFib, yet at the same time you can't really give them tPA.

Those are patients that we should consider for intraarterial, which we'll talk about in just a second here. And then blood pressure. There are some patients that you can't get their blood pressure down, but, for the most part, if you aggressively treat them with antihypertensive drips and what have you, you should be able to make most patients candidates from that standpoint anyway.

So who here has heard of three big trials that told us don't use intraarterial tPA or intraarterial thrombolysis? Basically, these just came out in 2013, SYNTHESIS, IMS III, and the MR RESCUE Trial. These are randomized, controlled studies that gave us very good data that intraarterial therapy and IV tPA are equivalent, and, therefore, the extra cost of the intraarterial therapy is not warranted. And it is randomized, controlled data. Again, it comes with a lot of value. However, like anything, you have to look at it critically and look at what it was actually testing for, OK.

The first thing that we have to know is that, like anything, when you start creating a study, and accruing patients, and then writing it up, it takes time. And so 2/3, over 2/3 of the patients-- when you combine all of these trials together --over 2/3 of them were treated only with a catheter and intraarterial tPA at a random dosing schedule. Between the three trials-- even within the trials --there was no hard and fast, we're using 20 milligrams of IA tPA or we're using five milligrams. It was just kind of random.

And so now what we're doing is a little bit different. We do mechanical thrombectomy, and there are one-third of those patients that did get mechanical thrombectomy with first and second generation devices. And we'll go over-- we're on the third generation now.

But it's just important to keep that in our heads. Now, that said, also very good wake-up call for all of us surgical types because we love to surgerize. To me, I would like to take everybody with a stroke and open them up, but that's not the right thing to do. So this helps us to select our patients a little bit better and also tells us we need to keep looking at things and figuring out who can we help the most.

So here is our first and second generation device. The MERCI is at the top. This was a great device when it came out. We have better now. It's a very stiff device. It lacerates vessels beautifully, and, obviously, when that is in combination with tPA, that's a major issue. So basically it's a corkscrew. You literally screw it through the clot and then you apply pressure and pull that clot out. As you screw it through the clot, pieces of the clot can break off. Sometimes it doesn't really take great hold.

That's the biggest problem with it, and, like I said, it's a little bit dangerous, all things considered. This was a clot up here that I took out about five years ago now. You can see. Pull that out of someone's M1, they're going to be much happier, as long as they still have viable tissue, OK.

This is a Penumbra, which is the device down here. So this thing-- this bigger catheter is a suction catheter, and this is the wire with a little ball at the end. So you basically put all of this under suction, arrest flow, put it under suction, and then you start taking this and going back and forth and back and forth through this clot until you're macerating it, which means you're beating it to little pieces, which breaks it up. It gets rid of your proximal occlusion. The only problem is all the stuff that's flying up here and lodging in the distal arteries where there is no good collateral circulation, so a bit of a mixed blessing. This is primarily what was being tested in these three trials. So just important to know about.

Now what we're using are stent-treivers, OK. And there's a couple different ones, but we will remain unbiased, with no disclosures, and just talk about stent-treivers in general. Basically you've got a catheter. You can use a balloon catheter or occlude with another balloon, but just some proximal occlusion. And you put this up and you basically mash this clot against the wall. You open it up immediately, which is a nice thing. You're already getting some perfusion.

My hardest part-- I have to be patient. I'm not very good at that, but we have to wait a good three to five minutes, get it well-enmeshed into that clot. At that point then, under suction, you pull that clot back. Sometimes it takes two or three passes, but almost always you can get this open. The rates of revascularization with stent-treivers are very good, up to about 88%, which is pretty impressive. Again, the question is, can you get there before the tissue dies. That's, of course, your biggest issue. So that's what a stent-treiver is.

All right. And so looking versus our first generation device, certainly things are getting better. The treatment time is faster with this, and you also have higher rates of good clinical outcome. Now, again, these are not completely stellar. Again, revascularization does not equal good clinical outcome, but we went and we started using IV tPA because that gave us 20% to 31%, and if we get 31% to 40%, that's pretty good.

I think that this tells us there are certain patients that are going to benefit. There are other patients that will not benefit. This is not a one size fits all kind of therapy, and we have to consider each patient individually. Very good. OK.

This is a patient that we used the stent-treiver on. Basically, they came in. We saw a large-vessel occlusion. They were out of the tPA window just by a little bit. So they were at four hours and 45 minutes. It's A1, but it's still a large vessel occlusion, but with one pass we were able to get this out and, thankfully, had a complete recovery.

Now for every story that I tell you with a complete recovery, as you guys know, obviously there's going to be a patient that has either an incomplete recovery or a problem, but I think that now we can do it with a good margin of safety. And I think we err on the side of being safe over using a device and trying to revascularize when we know that there's going to be a bad outcome.

The other thing that's very nice is that we can use the stent-treiver or a mechanical device in combination with that IV tPA. We give the IV tPA. If it hasn't started working-- especially if this is a telestroke that's coming over from another place.

By the time they get to us if it hasn't started working, we can go up there and put them into the MRI scanner, get a 15-minute perfusion scan, know if there's still viable tissue, and then use that device. Using this is a combination instead of isolated therapy.

This is just a case review, which I'm going to finish up with. It's a 60-year-old male. He was 3 and 1/2 hours from the onset of right hemiplegia and gaze deviation. He was an NIH Stroke Scale of 17. Again, good NIH Stroke Scale . Probably don't need tPA. Certainly if they're not getting better. But certainly don't need intraarterial, especially if they're getting better.

So, for me, if somebody is antigravity, they're not going to get intraarterial, because it comes along with risks. So this patient-- we had a CT brain. It was negative for hemorrhage, but there was a hyperdense MCA sign. They got IV tPA, full dose. There was no improvement.

We did a CTA at the same time as the CT, which showed this M1 occlusion. And then as we were looking back, there's also an ICA string sign, so I'll show you that. A CT perfusion shows a large penumbra and they were taken for an IA thrombectomy.

So here's your hyperdense sign. Here's your cut-off of the M1. Here is your perfusion or your cerebral blood flow. OK. So blue is bad. That means you're not getting the perfusion that you need. This is tissue that's at risk. So this is really not getting blood flow and this is not getting blood flow. OK. The first thing that we're seeing is your carotid. OK. This is on the left side. So here is your internal carotid right here. This is the external carotid.

You see that tiny little string right there? That's all that's left of the carotid. Very focal area, but because of that-- and this looks like nothing, and that's exactly what it looked like, nothing. So here's your internal carotid coming up-- and you can see --I mean there's really just no --there's no flow. Your ECA is filling much better than the ICA and it's because of this, OK.

The first thing we do is we angioplasty this open. Normally if you have carotid stenosis you either get endarterectomy or angioplasty and stent. In this patient, to put a stent we need to use antiplatelets, so Plavix and aspirin.

We don't ever know exactly what's going to happen with stroke patients and so if you have a large stroke area and you put them on aspirin and Plavix, you could potentially have a major disaster on your hands. So this patient we angioplastied open first, gave it several days, and then when we knew that they didn't have a stroke, went back and put the stent in afterwards. That was a pretty good strategy.

So we get that open. Now we have our ICA coming up. ACA looks great. Complete M1 cut-off. This is where we used the stent-treiver, and with two passes, we got this completely open, revascularized good capillary flow without any stasis. When we get stasis we know that some of that tissue is not acting normally.

All right. That's basically all I have for stroke. Other things-- we're new in the era of interventional and so there's a lot of stuff that we can do. Obviously carotid stenting, tumor embolization both in the brain, in the face. One of my projects that I worked on when I was in fellowship and have been working with is for juvenile nasoangiofibromas, and to be able to do those-- I don't know if you know much about those --they're not terribly common, but they happen in young males, teenagers, OK.

So 13, 14-year-old kids that start getting nosebleeds or what have you, and the classic surgery for that is dropping the midface and doing a Le Fort. This is a big deal for a 13, 14-year-old kid. Huge blood loss, huge time, wired shut jaw. Bad stuff.

And so we started working with ENT and basically going through the nose, sticking a needle in it it, embolizing it with Onyx, and then having ENT, in the same bout of anesthesia, go and take it out endoscopically. Kids were out of the hospital within one or two days and so neat stuff. And definitely stuff that I want to keep furthering and seeing what else we can do.

Carotid cavernous fistula, dural fistula. Certainly those are anybody that comes in with a big eye, certainly if there's a bruit in there, if they have intraocular pressure. Those are things that we can take care of very nicely endovascularly. Pseudotumor is another kind of untapped arena. We know that there's many reasons for this. Some of it is obesity. Some of it is sinus thrombosis. Some is narrowing or just stenosis of the veins and the sinuses. And so in some of these patients we've had really good luck with opening them up and stenting them open. Again, more things we can do and look at.

My final frontier is intraarterial chemotherapy, and it's something that is being used in various tumors throughout the body. We haven't figured it all out yet. We know that in GBM it doesn't work like we thought that it should, and that's certainly disappointing, but there's probably some good reasons for that. These are high-flowing tumors and so you inject some chemotherapy and it waves at the cells as it rushes by. So can we put a balloon in there, give it more time. There's lots of different things to think about.

One avenue where we have had really good-- this is another of my projects --but with retinoblastoma-- again rare tumor, but this is affecting the babies and you have a one-year-old or a two-year-old who's going to lose their eye and possibly their life from this tumor. That's a big deal, and you'll do anything to save them, but, unfortunately, that anything is looking at 9 to 12 months of IV chemotherapy, the bad kind, where you lose your hair, and you're throwing up. And this is a baby. You can't explain that to them.

We have been able to take a tiny catheter, go straight into the ophthalmic artery. And it does take an angiogram, and it takes a general anesthesia, certainly, but with one or two of these embolization or intraarterial chemotherapy embolizations, have been able to achieve the same results as a year of IV and cure a good number of these patients. There's neat stuff out there. I look forward to working with all of you guys.

Please. I'm happy to answer any questions now or later. That's it.