The Role of Surgery and Chemoembolization in the Management of Carcinoid

Presented by:
Rodney Pommier, MD, FACS
Associate Professor of Surgery, Division of General Surgery,
Section of Surgical Oncology
Oregon Health Sciences University
California Carcinoid Fighters Conference
October 25, 2003

It's a real pleasure for me to be here, and it's just fantastic that we have so many carcinoid experts speaking to you all on the same day. I wanted to be a surgeon ever since I was a small child and, of all the experts that are here today, just Dr. Woltering and I are the surgeons, but only I will be talking specifically about surgery for carcinoid disease. However, while I was in junior high and high school I started wanting to be an astronomer. In college, I was of course studying pre-medicine, but I was also studying astronomy. I'd pretty much completed all of the college astronomy courses by the time I left high school and started taking graduate astronomy courses in college. So, there came a point where I had a hard time deciding if I was going to be a surgeon or an astronomer. And life really comes down to a matter of licenses. I finally realized that I could be a great professional surgeon and a great amateur astronomer, but the other way around is highly illegal. So, I became a professional surgeon and an amateur astronomer.

So, why am I talking about astronomy at the beginning of my talk? Well, this talk will almost need one of those warnings that you get when you see an operation on television on the Discovery Channel and the like in that I'm going to show you a lot of pictures of operations and surgical specimens. So, this talk may be objectionable or disturbing to some viewers. This [slide] is a picture of my observatory at my home, and what I've done for years to break up the relentless bombardment of graphic surgery pictures is that I have punctuated my talks with astrophotographs that I've taken. I am going to take you on a tour of carcinoid surgery as well as of the universe. In the carcinoid realm, I'll start with primary carcinoid tumors and work up to advanced disease. In astronomy, I'll start in the solar system and working our way gradually out to distant stars. There are nice breaks between the surgery pictures this way. If the surgery pictures still disturb you, you can look away. If you're really light-headed, put your head between your knees like we do with medical students in the operating room. If it gets really bad, have someone escort you out. But, by having the astronomy pictures breaking up the talk, we're not just bombarding you (and I've had people under the tables when I've done this relentlessly).

Here is an outline of what we're going to talk about: we're going to talk about resection of primary tumors, the tumors that start out in the intestine, the lung, the pancreas and the like. Then we're going to move on to the concept of liver resections; we're going to talk about liver anatomy so you can understand what it is we're doing and then the liver resections themselves. Then, we're going to talk about chemoembolization and radiofrequency ablation. For that, we have to understand what the problems are with chemotherapy for carcinoid so we can understand the advantages of these other two techniques.

The old recommendation used to be when patients showed up with carcinoid syndrome and we found that they already had liver metastases, we really didn't perform any exhaustive search for the primary. Even if we knew where it was or we found it with our search, we didn't go after it. The belief was, then, that even though you lived longer with carcinoid than with other kinds of cancers, it was considered extremely unlikely that the primary tumor would give you a problem if it hadn't already. And so, we thought that we'd only go after that primary tumor if it subsequently causes problems of obstruction, bleeding, etc. Very few patients actually required going back for surgery to get their primary tumor with that old paradigm. But as we've shown you carcinoid patients are living longer. This [slide] is actually work by Dr. Woltering's partner Lowell Anthony. Lowell called me one day and

said that this was just the most exciting thing. Shown in a red line here is a survival curve showing what percentage of people are alive so many years after diagnosis of their carcinoid syndrome. And this is the classic paper from the Mayo Clinic that shows if you don't do anything except best supportive care, meaning fluids, antidiarrhea pills, things like that, 17% of patients make it 5 years with liver metastases. And to most oncologists who have patients with liver tumors that come from lung cancer, breast cancer and the like, there aren't any 5-year survivors. In fact, patients live about 6 months. So, boy, if you can get 17% of patients with liver tumors to go 5 years with no treatment, that's what they're doing is "no treatment". He actually showed that in the era of octreotide (he took his patients from Vanderbilt, an equal number) and you can now show that they have a 67% 5 year survival rate. That is proof that it isn't just palliative, it's therapeutic, as Dr. O'Dorisio showed you. I went and looked at our data at OHSU (The Oregon Health Sciences University) and found out that before we weren't even doing as well as 17% survival. We had about a 7% 5 year survival rate with best supportive care, but with octreotide we had a very similar 67% 5 year survival rate. So it's very, very real. Things have changed; the survival is now longer. It's not going to be true that if we just leave your primary tumor alone, you're not going to get in trouble with it. We believe that you will come back with pain, obstruction and , rarely ,bleeding and need surgery. The problem is that you're going to have a lot fewer complications of that operation if it's done earlier in the disease course when you're in better shape. There are studies by people like Dr. Öberg that show patients who have their primary tumors resected actually live longer. Now, that could be what we call a selection bias. In other words, if I can get your tumor out, it's probably a better-behaved tumor and therefore you do well. If I can't get it out, it's a big, nasty tumor and therefore you might not do as well. But, you can look at it from another point of view and that's that the quality of life of patients who have their primary tumors taken out when they have cramps and pain is also better. And, we also have the probability of relieving hormonal effects of the tumor. Now, I'm going to show you a graphic example of this.

This [slide] shows Harry. Harry had a lung carcinoid tumor that besides making the serotonin that causes flushing and diarrhea also makes a hormone called ACTH. As we've described, carcinoid tumors have incredible genetic memory and they can make any peptide hormone that is extant in the human system. This tumor makes way too much ACTH, which also drives his adrenal glands to produce too much cortisone, and you get Cushing's syndrome of obesity. When Harry came and saw my nurse Pam and I, he was bound in a wheelchair. He'd lost so much muscle mass from his legs and his arms that he could no longer walk, and you get trunkal obesity and you get a big, flushed moon face. I asked him for some pictures, and he actually didn't have any recent pictures, but he went back and dug up this picture. [In this picture], he's already having difficulty walking, he's gained a lot of pounds, you can see the big, red moon-shaped face. The problem was, I couldn't find his primary tumor. So we had to watch him for a while. We knew it must be in the lung because it was making ACTH. This [slide] is a CT scan going through the middle of his chest, and here is where the bronchial tubes arise, all of this black area out here is his lungs. This CT scan was actually read as normal by the radiologist, but I want you to keep your eye right there. There is a little nubbin in there that we would have called negative, but when we scanned him a little while later you can now see that thing has gotten bigger. We said that's a good indication that this may be where this tumor is. It's always good if we can confirm where the tumor is by more than one modality, so we did an OctreoScan [slide]. He's lying on his side; here is his diaphragm on the right side, and diaphragm on the left side. His head's over here, and his feet are over there. But there is just a little bit of uptake right there in that lower right chest which corresponds with where that finding was on the CT scan. So I then did what's called bronchoscopy, taking a little bendable telescope, going through his windpipe, and down through all the bronchial tubes one at a time. When I got way out far, here [slide] was this little, chick pea-sized tumor in a bronchial tube. That is a normal open bronchial tube, and this one's blocked, and this was a chick pea-sized tumor causing all this hormonal effect. So, I went ahead and operated, took out that lobe of the lung. And that [slide] is Harry after his operation when all the hormonal effects have gone away. So you can see it's very, very dramatic what can happen with carcinoid patients and removing their primary tumors.

Well, this [slide] looks like a full moon. It's not; it's actually the beginning of a total lunar eclipse. What's visible here is not the dark side of the moon, but this is the moon creeping into Earth's shadow and it's gradually blocking it out. As an hour goes by, you can see the moon essentially looking like it's being swallowed up in darkness. This is what the Chinese and the Thai were very scared of. They believed there was a giant dragon in the sky that was eating the moon and the sun

during eclipses. It just gets more and more progressive. You can't see anything in this part of the moon in Earth's shadow. Eventually, you get really frightened that the whole moon is going to disappear. But, actually, it doesn't. When the moon moves completely into Earth's shadow, it turns this beautiful coppery red color. That's because if you were actually standing here on the Sea of Tranquility and looking back at Earth, you wouldn't see the sun blocked out. You'd see a nice, red ring going all around the Earth, which is the sunlight refracting through the atmosphere. Every sunset and every sunrise that's happening at Earth gets projected onto the moon and makes it this lovely red color. It's really very beautiful. The nice thing about lunar eclipses is that they're visible from half the earth and there's one coming up on November 8th [2003]. They take about 3 hours, an hour for the moon to move in, an hour for it to go through, and an hour for it to come out. And they're totally free admission, so sit back and watch the next lunar eclipse on November 8th. It'll be widely visible in North America. On the west coast here, the moon is going to rise, partial eclipse, but you'll get to see totality.

Now, some patients actually come in with bowel obstruction as their first finding. This is a typical course, where the patients have been misdiagnosed for years with irritable bowel syndrome, food allergy, food intolerance, and some people are labeled as just plain crazy because they go to the doctors and nobody can find out what's wrong with them. But then, there's a fork in the road, where patients will either come in with small bowel obstruction or they get liver metastases with carcinoid syndrome, and then you'll find the tumor. We have to operate for small bowel obstruction very frequently when these patients happen. This is a little difficult to figure out, but it takes a lot of judgment to determine how much intestine to take. There is actually 35 feet of small intestine going from the end of the duodenum down to the colon. It's cartooned here [on the slide] as being very, very small. We want to take as little intestine as possible.

This [slide] is a primary carcinoid tumor in the small intestine; it's this little white thing right here. This patient came in with carcinoid syndrome with flushing and diarrhea. There is probably about 5 pounds of tumor in this patient's liver, and yet here is the primary tumor that started it all. It never ceases to amaze me how small the primary can be and how the metastases in the liver can outdo it by magnitudes. So for this, we just resected the intestine like that, take that out and put the two ends back together to avoid an ileostomy or colostomy. Here's another tumor in the small intestine. You can see that when they get a little more advanced they start causing this kinking and turning of the bowel that causes the crampy, nonspecific, vague abdominal pain. And again, we would just resect this. But there is another problem: these are some of those milliary, sesame seed-sized metastases that Dr. Warner was talking about as one form of spread. Besides having this primary tumor, there has already been spread to the peritoneal cavity.

Here is another tumor causing cramping and abdominal pain. You can see the kink in the bowel. The other thing that you notice about this is that this is the normal color of the small bowel here, nice and pink and healthy-looking. This part of the bowel here is experiencing flushing even though the patient isn't having any flushing on the outside because they don't yet have liver metastases. The bowel itself is flushing because of the hormones being released. And patients will tell you that when they flush they feel bad. Actually, before patients get symptomatic flushing of the whole body, they kind of feel bad in the abdomen. I think that's because they're actually having internal abdominal flushing for many years before they get carcinoid syndrome. Here is yet another tumor. Once again, you can see the profound difference in the color between the bowel that's being affected by the hormone release and the normal bowel that's farther away from it.

Resecting carcinoid bowel tumors takes a great deal of judgment, because carcinoid hormones cause this fibrosis of the peritoneal cavity in that it causes bending, folding and kinking of this sheet that the intestines are suspended on called the mesentery. Normally, the peritoneum on the outside of this mesentery is about the thickness of Saran Wrap. With years and years of a carcinoid tumor being present and the hormones being released, it can get as thick as shoe leather. Here is a picture showing the sheet called the mesentery and you can see how it normally looks. Now here is a patient who is coming in with total bowel obstruction. These are not normal looking bowels; they are big and dilated. You can't even see the mesentery; it is so folded and convoluted like accordion pleating that you can't see it. The tumor is actually down inside here. The question is, how am I going to get all of this out without getting all the mesentery that affects supplies blood to the bowel? It's a real difficult judgment call. If I take out too much bowel and sew the two ends back together, then you give the

patient what's known as short bowel syndrome. Short bowel syndrome lets your food go right through you, on to your colon, and results in diarrhea. Even if the patient doesn't have carcinoid syndrome yet, they might get it later on. A lot of these patients, as I've said, already have carcinoid syndrome, and diarrhea from short bowel syndrome on top of diarrhea from carcinoid syndrome is a terrible combination. It's a real conundrum of how bowel much to resect. Resecting too little bowel can compromise the blood supply, and when you sew the two ends together you're dealing with a tangled, folded mesentery, and the blood vessels in there aren't in very good shape and the bowel may die. On the other hand, if I take out too much, I may give the patient short bowel syndrome. This [slide] is what I removed; this is about 5 feet of the bowel. All the rest of it I left inside. Here is a little bit of the beginning of the right colon. That is enough to relieve the obstruction, relieve the symptoms, but leave the patient with a decent amount of bowel so that they won't have short bowel syndrome.

There are times when it's just not safe to resect. The tumor may be too big, too extensive, and so the goal there is to relieve the obstruction and the pain. I usually try to do that by finding intestine before the tumor that is normal and intestine beyond the tumor that is normal, and sewing those two portions together in a side-to-side fashion so the food can go completely around the tumor. Now, for a few months after that, there is still going to be food trying to go through these convoluted hairpin turns of the bowel. But with time, the gut learns to just take the easy path through the bypass, and the food goes around the partially obstructed bowel and the pain gets better or goes away. There are times when I can't even do a safe bypass, and then what I have to do to relieve the obstruction is cut the intestine in half, bring it to the outside, and give the patient what is called an ileostomy or a colostomy to let the bowel contents come to the outside and get rid of that obstruction.

Well, lunar eclipses are free, but total solar eclipses are not. They are very expensive. They go through a narrow slice of the earth about 60 miles wide and a couple of thousand miles long. That's why I had to go to Turkey in 1999 to see the solar eclipse that Susan Anderson mentioned in my introduction. This is the sun. People ask how I take pictures of the sun. It's easy; you just do it at night (no, that's not true, I use a filter that blocks out 99.999% of the sunlight). These are sunspots, which are giant magnetic storms on the sun. This sunspot is bigger than the planet Jupiter, in fact. There was talk yesterday about cellular phone service going out in California, and that's because of solar storms arising from sunspots like this one. This is a solar eclipse from Turkey, the one that I was almost killed trying to photograph because of the earthquake that occurred. This is the sun in totality, during which you actually get to see solar prominences which are these giant flames of plasma leaping off the sun near sun spot groups. This is the corona. It's a very, very hot solar atmosphere. It's the only place in the universe where we know something very strange happens: normally when you have a log in the fireplace or a pot on top of a stove, the thing on top being heated is cooler than the thing doing the heating. It's not the case with the sun's corona. The sun's about 800,000 degrees, and the corona is at 2 million degrees. We just don't even know how something heated by the sun can be hotter than the sun itself, but that's the superhot corona stretching out into space. This goes all the way to Earth and causes auroras and interference with our phones and things like that. So, that's was the solar eclipse in Turkey. There's also a solar eclipse next month in case you want to go. The sun will be blotted out for a mere 28 seconds in Antarctica. The next one that touches land after that is back in Turkey in 2006. I'll be there for that one, and hopefully there will be no earthquakes.

Now, pancreatic primary tumors are a little bit different to deal with. When I was in residency we learned three rules of surgery: eat now, sleep when you can, and don't mess with the pancreas. The reason that you don't mess with the pancreas is that it's not just an endocrine organ that makes hormones, it's also a digestive organ that makes enzymes. These enzymes break down muscle in terms of steak and chicken, and they break down fat in terms of nachos, ice cream. If the pancreas leaks after surgery, these enzymes get loose in your abdomen and guess what? That's what you're made of is muscle, fat, and so it starts digesting you and it can eat you up. It can be a very, very serious complication. Well, I can tell you that as a surgical resident I am pretty good at eating now, although not as good as Dr. Woltering, as an astronomer and a surgeon, I don't even pay attention to the rule of sleeping when you can. And, as an endocrine surgeon, I blatantly and intentionally violate the rule about not messing with the pancreas all the time.

So, there are pancreatic carcinoids. Here's the pancreas; it lies sort of between the stomach and the

colon. Here is a CT scan. I want you to get used to what normal livers look like on CT scans. This is a normal liver. Here's the pancreas draped across the spine, here. But look as this: there's a golf ball-sized mass in this pancreas, and that's actually this patient's primary carcinoid tumor. We could not find any evidence of metastases in this, and so yes, we're going to violate rule #3, go in and mess with the pancreas to get that out. Here I am in the abdomen, here's the stomach, there's the colon. The pancreas is draped right across here, and you can see this golf ball-sized tumor. There's the liver right there. Those big veins out of it are draining the hormones right into the bloodstream. Most of the time what we can do is just take our little 9-iron and wedge these things out. I put a stitch in the tumor here as to help me put traction on it while I'm removing it so I don't squeeze it with my fingers and cause massive release of hormones during the operation. You can see this black string, and I'm sort of teasing the tumor off the pancreas and trying to seal the pancreatic ducts as I go along so that we don't get a leak. That pancreatic tumor came out just fine and the patient did great.

We're moving out into the solar system. This is Jupiter. Jupiter is big enough to hold 360 Earths inside its volume. It's got these incredible cloud belts. These blue zones, called festoons, are actually water vapor molecules that you can see on it. I'm still trying to get the perfect picture of Saturn. Saturn has this little black gap in the rings known as the Cassini division. Every single picture I've taken has had a blurry Cassini division, but someday I'm going to nail that. This past August, Mars was closest to Earth that it's ever been in the history of the telescope. The heat waves in Oregon were horrible. Mars is tiny even through a telescope; you can see the difference between it and Jupiter. The photographs are of the same scale. But still, on a good night, like when I took this photograph, you can see the south polar cap here made of snow. Here are the famous canal markings, which are actually just sort of dark rocks on Mars.

Having surgery when you have carcinoid can actually be dangerous. There is a problem known as carcinoid crisis. Carcinoid crisis is caused by excessive release of the carcinoid hormones at the time of surgery or any other time, for that matter. It starts out with dangerously high blood pressure caused by hormones squeezing your blood vessels shut. Then, it's followed by dangerously low blood pressure, as your blood vessels relax. So you get blood pressure that on the little sphygmomanometer reads, "Patent Pending. Over 300." Followed by, "0". It can also cause very severe bronchial constriction so that you have a problem getting oxygen or being ventilated if you're in the operating room on a respirator. And it can result in death.

The problem is that certain anesthetic agents and drugs that we use in the operating room will trigger release of the hormones and therefore have the potential of causing carcinoid crisis. Other factors that can trigger it are having a low body temperature when you have your abdomen or your chest open. There are a lot of evaporative losses and cooling going on so your body temperature can get too low. If we're losing too much blood and we're not keeping up with the blood volume, then the sympathetic nervous system kicks in trying to bring your blood pressure up. As a side effect, that'll trigger hormone release. Pain will also trigger this. We ought to have that as one of the Five E's that trigger carcinoid hormone release and carcinoid syndrome: eating, exercise, emotion, epinephrine etc. Surgical pain will definitely trigger release. And then, I'm part of the problem. I'm trying to handle this tumor, and if I squeeze lymph nodes or move things around, or just even pick the tumor up and cause it to be in a more elevated position, hormones will just drain out by gravity. And this can trigger a carcinoid crisis.

This is a patient on the operating table having a carcinoid crisis. He was so hot when we took this picture, that it felt like he was actually heating the room. He was just that hot and all purple, and the blood pressure was very, very high followed by the blood pressure going very, very low. So, you really need to have a good team if you're going to have carcinoid surgery. You have to have a surgeon and an anesthesiologist that are experienced in operating on carcinoid patients and know all these things. The most important thing is that you need to have excellent communication between those two. They have to know what each is doing at all times. If the anesthesiologist just had to give a drug that might be a little bit dangerous for triggering crisis, that's not a good time for me to start handling tumors. So if we're not talking to each other, we could both be doing something at the same time that could cause a carcinoid crisis. Before patients go to surgery, we frequently give them a dose of antibiotics to prevent infectious complications. I always give carcinoid patients an extra dose of Sandostatin, even if they're on LAR, about 300-500 mcg subcutaneously going into the

operating room. I also get several glass vials of short-acting Sandostatin and take it into the operating room with me and hand it to the anesthesiologist. I say, "In case of emergency, break glass". If a carcinoid crisis is triggered, we can break a carcinoid crisis by giving Sandostatin and it can be life-saving at the time of surgery. But you need to know this. You may all end up having to have your gallbladder out or having a hernia fixed or something like that, and it's very important that you let your anesthesiologist know about this. You need to get somebody who's experienced with it, if it's elective surgery. If it's emergency surgery, you have to have it tattooed across your chest, "Give Sandostatin before surgery".

Here are some more solar system interlopers. These are comets. We've been lucky; we've had two fantastic comets come through in the last decade. This is Comet Hyakutake. This guy named Hyakutake in Japan was looking for comets and he saw this fuzzy spot that he thought might be a comet. The way you tell that it's a comet is it keeps moving from one night to the next. Well, he kept looking at it night after night after night, just waiting to report a comet. The only thing in the universe that you can name after yourself is a comet. Everything else gets named by the International Astronomical Union. Well, this fuzzy spot Hyakutake saw just didn't move, and didn't move, and on the sixth night he realized that it's a comet alright, but it's not moving because it's coming right at Earth. That was why it didn't wasn't moving. So, it actually buzzed the North Pole by a mere distance of 2,500,000 miles which is pretty darn close in astronomical terms. This [slide] is at it was buzzing by the North Pole of Earth. This is the Big Dipper right here. You can see it going by like that, so this tail went 80-90 degrees across the sky. It was really a spectacular comet. That was followed by Hale-Bopp, which here is taken through the telescope. To have two comets a year apart like that was really fantastic.

Moving on to liver resections. In order to discuss this, we need to know a little bit more about liver anatomy, as well. For patients with carcinoid tumors, they may develop isolated liver metastases. That's not the norm; usually we have patients that have multiple liver metastases. There is a subset of patients, though, that will get isolated liver metastases and that's it. That's their only site of disease. The primary tumor may have been resected, they have had a disease-free interval between the time of their primary surgery and the metastases showing up. But if you leave these tumors here, such patients are likely statistically to die of carcinoid disease. If a patient has isolated liver metastases, a liver resection may, in fact, be curative. With a disease that has a very long life span even without surgery, it's difficult to use the word "cure" because these tumors may show up 20, 30 years later again, and then they weren't cured. But, compared to colon cancer, this is a much better outcome. Even if they're not curative, the big thing once you have liver metastases are the symptoms of the carcinoid syndrome that, as Drs. O'Dorisio and Warner explained to you, happens with the tumor in the liver. It does not really happen with tumor in the gut because the liver filters the hormones out. If we take these isolated liver metastases out, we have patients that have very long, disease-free intervals where they really don't have the symptoms, even if they get more liver tumors later, so it's worth doing for that reason alone.

Now, we can remove liver because of several reasons. One is that God gave us all 85% more liver than we need to stay alive so we can take out a great deal of it. And, the liver is the only organ in the body that regenerates once you take it out. If I take out 10 feet of intestine, it's gone. If we amputate your left arm, it's gone. If we take out 85% of your liver, it's cells starts dividing in the first 24 hours, and after one week the division is going at warp 9, and at six weeks, that liver has completely replaced itself. The only deal that's better than that is a haircut. So, resections can even be repeated. If you have part of your liver taken out, it grows back and you get another tumor in that part that's grown back, you can resect it even a second time.

Let's go over how we do these liver resections. For this, we're going to need to understand liver anatomy. Now this [slide] is a sort of cut-away or an inside peek of the liver. It classically has what is known as a right lobe on the right side of the gallbladder and a left lobe on the left side of the gallbladder. There are three different things that go into the liver at the bottom. There's the bile duct that drains the bile from the biliary tree down into the intestines. This is the giant portal vein that drains all of the guts in the abdomen. The portal vein is, in fact, how carcinoid tumors travel from their primary site in the GI tract up to the liver, and then they get stuck in these peripheral branches and they start growing. Then there is the hepatic artery, which is a skinny, spaghetti noodle-sized artery that goes in here. The liver gets about 80% of its blood and half the oxygen from the portal

vein, and only 20% of the blood and the other 50% of the oxygen from the artery. These things branch and branch and branch all over the place inside the liver. Then, the blood gets collected from the liver tissue and goes out these hepatic veins back into the vena cava and into the heart. This is what's known as the right hepatic vein, which I surgically describe to my residents as the biggest, fattest, closest to the heart-est vein in the whole body.

Now, if we inject these structures down here with latex such as blue latex in the portal vein and red latex in the hepatic artery, and take that liver and drop it in a vat of lye so that all the flesh gets dissolved, but the latex doesn't, you would get latex casts of the inside of the liver vessels. And this is such a cast. You can see that the liver's just a huge sponge of blood vessels. Who would want to go through the liver right here? You're just going to have a blood bath. But there are planes. The liver is actually made up of about eight different segments of liver, and they're subdivided in different directions. There are these actual cardboard sheets that are inserted in between these planes in this cast, where you can get it right through because it's where groups of blood vessels come up and touch each other, but they don't cross very much. So there are planes in the liver through which we can resect to get tumors out without hurting the ductal structures or incurring much blood loss.

There are eight different segments in the liver, and if we take out all the stuff on this side of the liver, we can take out about 60% of the liver and leave three of these segments over here behind at the left lobe. This is called a right hepatic lobectomy if I go through that plane. If, on the other hand, I do the reverse and take out the segments on this side and leave these four big segments over here, we have a left hepatic lobectomy. That removes about 40% of the liver. If I take out all the segments except these two little ones over here, this is called a right hepatic trisegmentectomy. That takes out about 75-80% of the liver, leaving you with only 20%, a little bit above that 15% margin that we talked about. And then there's a very complex, difficult operation where we take out everything on the left side except these two segments. That's called a left hepatic trisegmentectomy, and we can take out 70% of the liver. This one's a little hard for people to understand, so if you look at the liver from the bottom, we take out all of this dark shaded area and just leave these two segments there. A lot of people go see surgeons about potentially having their hepatic tumors resected, and the surgeons they see may say, "Well, there's two or there's three different tumors and they're on different sides of the liver, and you're just not resectable." And that's not necessarily the case. You've got to know your liver anatomy and really understand it in that you could have all kinds of disease here, but if there's nothing there, you could potentially still be a candidate for a liver resection. You could have a left trisegmentectomy and get all the disease out and leave only normal liver behind. Lastly, we can take out these two little things. It's just sort of a chip shot once again done with the 9-iron and that takes out 20-25% of the liver. That can be combined with a formal hepatic lobectomy. A combination of a lobectomy and a wedge resection can render people free of tumor that would otherwise be considered as unresectable.

Moving from the solar system into our galaxy, these are some of the nebulae that are out in the sky. These are actually stellar nurseries. These are areas throughout our galactic arms in which there are giant clouds of hydrogen gas, and they condense. As they start condensing they turn into little globules of things called Bok globules. Eventually, the pressure in there from the gravity starts causing nuclear fusion at the core of this, and boom! A star is born. All these are stars that have emerged out of this nebula over of the past several millions of years. The sky is just filled with these things. This is called the Eagle Nebula. If you want to look at the little astronomy picture that is on some of your peoples' name badges that shows dark pillars of gas clouds, that feature is that little black thing right there by that star. There is another star that's just born. And eventually, as these stars are born, they create this solar wind, like the corona that was coming off the sun during the solar eclipse. That actually blows away the pink hydrogen gas, leaves behind a whole bunch of blue dust that is left around the star, and that's what coalesces into planets.

So let's talk about a patient who's going to have a liver resection. This, once again, is a fairly normal looking liver in a patient who had a carcinoid tumor of the small bowel, but it's not completely normal. These are blood vessels in here, but that thing right there is a tumor. It's pretty deep inside and it's pretty close to the portal vein. So what we would want to do is do a resection right through this plane between the right lobe and the left lobe, and take out the left lobe to get that tumor out, leaving all this normal liver behind. The question is, how do you find that plane when looking at a

liver because it's just this big, brownish thing inside the abdomen? Well, what you do is you go inside here and you have to dissect out this region of the liver, and you divide the left hepatic artery going to the left lobe. You divide the left portal vein that's going to the left lobe. And you divide the left bile duct going to the left lobe. Then you come up here and you divide the veins that are going to the left lobe. And when you actually do that inside, you start seeing a color change inside the liver because you've cut off the blood supply to one half of it. You can sort of vaguely see there's a line right there, but here it is with my forceps pointing at it. There's this beautiful line that shows up that basically says to we surgeons, "cut here". That takes about three hours of operating time to get that all dissected out and arranged, but then you actually go through the liver in about 15 minutes' time dividing any little vessels that are in the way with clips and sutures. Then comes the Star Trek part. We get out this really cool thing called the argon beam coagulator. It shoots this beam of plasma and basically seals the surface of the liver. One time I had a medical student and I let her fire the argon beam coagulator at the liver. I said, "Isn't that just the coolest thing?" She said "Well, it's kind of okay." So I took it away from her instantly, and said "You've got to think it's cool or you can't run it." It was just wasted on her! So here's the left lobe of the liver. There's the tumor, the typical yellowish color of carcinoid tumor. We've got plenty of margins in all directions around that. This patient has been disease-free ever since. No problems, no carcinoid syndrome, Chromogranin A's are all normal.

Let's look at another thing. With patients that have disease over here in the left, we can just go through that plane and that's what I said is a pretty easy thing to do with the 9-iron. Here is the left lateral segment of the liver with an enormous tumor in there. Basically, just take that part of the liver out and that is a clear and free way to go. Here is another patient. This all is the right lobe of the liver. Here is the left lateral segment. It is not normally this thick; normally it's about as thick as your hand. This is greatly thickened because there is tumor going from the front all the way to the back. You can't really see all of the tumor that is bulging out of the back side of here, so we lift it up and those are the burgeoning tumors on the bottom. But once again, over here, the liver is all normal. The gallbladder is nice and healthy. If we just lop this off, we can make this patient free of carcinoid disease in the liver. There is the specimen there; we've got great margins over here. That tumor is all out, as well.

Sometimes patients just have small Jawbreaker-sized or walnut-sized tumors on the surface of the liver, and you can do what are called wedge resections of the liver rather than a complete lobectomy. Lobectomies are big, they're massive. It takes a lot of coordination and work. So, we can do small wedge resections around a tumor and that saves a lot of liver tissue. We don't have to worry about the patient having hepatic insufficiency for a period of six weeks after the liver resection, there is less blood loss, etc. But it's only appropriate for small tumors on the edges of the liver. Large, deeper tumors are really best treated with lobectomies, in which case you have better control of blood vessels and ducts during the resection. There are reasons for that. These are tumors that are on the edge, on the periphery of the liver. They are small and for such tumors, I don't really want to do a whole left lateral segmentectomy or a whole left lobe if I can just shark bite that out. And same thing here: instead of doing a complete right lobectomy, we can just wedge that out. But you've got to be careful. The problem with the liver is that the deeper you go, the bigger the blood vessels get. And when we do a wedge, it may look like this is an appropriate lesion for a wedge resection, but it's not, nor is that one. That's because when I start out on the surface, it seems like I've got plenty of margin from there to there, but wedges are wedge-shaped, like slices of pie. You can see that as I come in, I'm going to get closer and closer to the tumor and actually might leave tumor on the edge of where I want. Then the big conundrum is that I get into the big blood vessels down at the tip of the wedge. And down here, I'm in a narrow chasm, I don't have good exposure, and if I get into a giant blood vessel in the center of the liver, and the blood just comes pouring out. So, a wedge resection for this tumor is not a good choice. What you're doing by taking a wedge resection here is that you're trying to save all this liver out here or all this liver here. But guess what? With that blood pouring out of the large vessels at the apex of the wedge, I've got to do something about it. So I get out my #10 Volkswagen towing cable-sized sutures and I go round and round and round that vein, and I tie it down. What I end up doing is closing that vein off completely. All this blood supply to this part of the liver is gone, and that liver dies. I didn't really save you anything. In fact, you can get into complications with dead liver left behind after this. So these tumors are not good choices for wedge resections. These are better dealt with complete formal lobectomies.

These are some appropriate wedge resections. This patient had a little tumor out here on the right

edge of the liver. I just took it off, took the argon beam coagulator to it and I was done. I also had a much more appreciative medical student that day, who thought the argon beam coagulator was the coolest thing she'd ever seen. Here is a tumor on the surface of the liver. This is resection that is about the size of a baby block that I took out. The tumor was right there in the center, and we just argon beamed the surface. All the rest of the liver was saved. Here are the two specimens. That is the one taken off the edge of the right liver, and here is the one that was taken out of the middle. If we just bisect those specimens, you can see the carcinoid tumors inside. We get them out with enough margin and it's very safe. We save a lot of liver and make the patient disease free.

Now, there are rules that most oncologists and most oncologic surgeons have about doing liver resections. They are derived from colon cancer, not from carcinoid. So once again, if you're being considered for potential liver surgery, you might get bumped out of the race because someone says you just don't qualify. So these are the rules that we've developed. You've got to have a limited numbers of tumors in the liver. Most people say up to five. The remaining liver that you're leaving behind after the resection must be completely free of disease. If they're leaving colon cancer in the other lobe of the liver, it's going to kill you anyway, and there's no reason to go through the risk of a liver operation. And, you've got to have great margins. Generally, they want at least a whole centimeter between where you cut and where the tumor is. If you have something less than that, they think that they cancer will just be creeping across that line and coming back. Now, the point for you to remember is that none of these rules really apply to carcinoid. In fact, we can bend these rules a considerable amount. It really isn't possible to put an upper limit on the number of lesions we can resect as long as we think we can get them all, or in some cases just most of them, out. And the margin of resection doesn't have to be wide or even clear. Because what we're chiefly trying to do in some cases is get the majority of the disease out, debulk it, and get your symptoms under control. That's the difference between a patient that has colon cancer in which they really don't get any symptomatic relief when we take their tumor out. The only benefit you can get is if you get all the tumor completely out and you live longer. But a carcinoid patient will get symptomatic relief if we take the tumor out, even if it isn't the best cancer operation in the world. I don't have to get it all out; I just have to decrease it in volume to cut down on the symptoms. And for that purpose, the remaining liver doesn't even necessarily have to be clear of tumor. If you've got a lot of disease on one side of your liver causing symptoms and making you miserable and there happen to be some tumors on the other side of the liver, I can still resect you and get you a lot better.

This is an example of a patient from Olympia, WA who really had severe carcinoid flushing. This guy was on about 60 mg of Sandostatin LAR every three weeks. He took 10 Imodium pills with each meal. Still, he was having voluminous diarrhea any time he touched food. He was a miserable cookie. Here's his CT scan, and what you can see is that he's got this enormous tumor over here in the left lateral segment. The remainder of the left lobe is pretty well dotted with tumors. He actually had his left hepatic vein on other cuts that was just this pipeline coming out of that tumor right there going straight back to the heart. That was what the source of the severe syndrome was. Now, if you look at his right lobe, yes, he's got a lesion over here. And on other cuts he had other marble-sized to chick pea-sized tumors, maybe four or five. But this is the problem: there's all this disease on the left lobe that's draining straight into his heart. So, I said, "I think we should do a left lobectomy on you and no I'm not going to get great margins, and no I'm not going to render you completely disease free, but we can make you a lot better". So, here we are in the operating room. Here is this enormous tumor in the left lateral segment. Here are those other ones that are scattered through the remainder of the left lobe. We took that out. There is that big tumor. Here are the other ones. And yes, I saw a couple things like that and that on the right lobe, but it really wasn't very much, and the improvement he experienced after the left lobectomy was absolutely dramatic. He went down to 20 mg of LAR. He stopped taking Imodium. And his flushing was no worse than any of the other well-controlled carcinoid patients that we have.

Now, later on as these stars start blowing gas away from the nebula, they get left in a lot more blue dust. The blue dust even gets blown away with time or coalesces into planets. Then you get these star clusters. There can be hundreds and hundreds of stars that are born inside a single cluster. This is one of my favorites. This one is called the Owl Star Cluster. You can see the two eyeballs, a wing here, a leg there, a branch down here. Yeah, you've got to have a lot of imagination to see constellations, don't you? What happens with time, though, is that these stars start fusing hydrogen and hydrogen into helium, then helium and helium into carbon, carbon and carbon into silicon. When

they start fusing helium, they turn into red giant stars. The sun's going to do that in about 4 billion years, and when it does it's going to expand so it'll eat up Mercury, Venus, Earth, Mars and go partway out to Jupiter. The real estate on Jupiter's moons is going to go up in value considerably at that time. And Hans Behta was the guy who figured out these nuclear physics reactions that fuel the stars. I remember he was giving a Nobel lecture once about that. He had a very heavy German accent and he said that he figured that the sun had about 4.5 billion years left to go until this happened. And then he finished his lecture and asked if there were any questions. This guy said, "Excuse me. Did you say 'million' or 'billion'?" years until the sun expands, because he couldn't understand the German accent. Behta answered, "I said 'billion'". The guy asking the question sat down and said, "Oh, I'm relieved".

Now, in reality, like I said, it's a pretty small subset of patients with liver tumors that can have resection. Many, many more patients have extensive liver disease all over the liver that does not make them an appropriate candidate for any kind of a liver resection. So for these patients, we've developed a protocol. This is something Gene Woltering and I started at OHSU and I kept working on it and perfecting it after he left. We actually used a combination of not just chemoembolization, but chemoinfusion followed by chemoembolization. These are examples of patients who you can clearly see are not candidates for liver resections. They just have cannonball metastases, ping-pong ball-sized tumors, all over the liver. There is no way to render this liver disease-free or even disease-reduced by doing a partial liver resection. The metastases are just all over the place. There are big ones, they become confluent after a while; there are little dotty ones. Again, there are too many to deal with all over the liver. We've had problems with chemoembolization alone. Chemoembolization is not a benign procedure. It has significant side effects of pain, nausea, weakness; it knocks down your liver function for a period of time. I'm looking at people I've done it to and they're glaring at me. But the problem with chemoembolization alone is that the response is not durable. We know that if you get chemoembolized, you'll have some improvement for a period of maybe 6 or 7 months, and then the disease starts growing back again, and so you have to repeat it. These patients are going in for this unpleasant aspect of the procedure repeatedly.

Now, there's a reason that systemic chemotherapy (chemotherapy that they put in your arm veins and let go all over your body) doesn't work very well. That's because chemotherapy attacks rapidly dividing cells. That's why the other rapidly dividing cells in your body like your hair, your bone marrow, your GI tract, your mouth lining, get significant side effects from this. The chemotherapy drugs, when they get injected, even though someone will lose their hair for months or their blood counts may go down for months, that effect is put in place in about 6 hours' time. Your body identifies chemotherapy as toxic, and the liver and the kidneys label it for elimination and get rid of it as quickly as possible. But it's the fact that just during these 6 hours, these rapidly dividing cells were hit by the chemotherapy that you get these prolonged side effects. It takes that long to recover. Now every agent under the sun has been tried against carcinoid. They've tried 5-FU, streptozotocin, doxorubicin, etc, and we consistently get the same thing. To get an objective tumor response, which is defined by oncologists as that the tumor shrinks by 50% of more from its original size, vary in these studies from occurring in 0% of patients to a maximum of 30%, with about 15% being the average that we see. That's because the carcinoid cells grow slowly and really aren't likely to be dividing during those 6 hours when the drugs are in your system. This is the down side of having a good tumor that isn't very aggressive. There is also a problem with timing. This is a concept that's coming out in oncology known as "chronotherapy". "Chrono" means time. It turns out that if you do studies, the enzymes that eliminate drugs are actually active in the early a.m. and are least active in the p.m. The enzymes that repair DNA damage, in other words, if a drug gets into a cell and damages the chromosomes, there are enzymes that come in and try to repair that damage to restore the cell to health, and we don't want that to happen in the cancer cells. Well, those enzymes are also most active in the early morning, and they're least active in the evening. On the other hand, cells divide most actively in the evening. So, basically, most people go in and get their chemotherapy drugs in a clinic at 9 in the morning, which is just the wrong time. So this concept of chronotherapy has been developed, of trying to give the drugs at the right time of day when the enzymes that repair things are least active, the cells are most likely to be dividing and get hit. That takes a very smart, if not, at least, a very dedicated oncologist.

We are taking a different approach with the carcinoid tumors that involves good chronotherapy. This is one of hepatic arterial infusion. If you look back at the liver, although it has two separate blood

supplies, the portal vein and the hepatic artery, the liver gets 80% of its blood from the portal vein and 20% from that little hepatic artery. But tumors get 100% of their blood off the hepatic artery, and this has been shown by multiple lines of evidence. Once again, if you take the liver of a patient who has died of tumors and you make a map of where all the tumors are, and you inject the portal vein with blue latex and the hepatic artery with red latex, drop it in a vat of lye and wait for it to dissolve, the portal vein tree that comes out is completely normal. The hepatic artery has fruit hanging from the branches, and those are where the tumors were. So that's evidence of where that they get their blood supply. If you do an angiogram where you inject the portal vein, you don't see anything coming off of the branches of the portal vein. If you inject the artery, you see the tumor blush, and I think it was Dr. Warner who showed a picture like that. Lastly, we used to do radioactive studies where, when I was in the operating room, we would inject the portal vein with one radioisotope and inject the hepatic artery with another radioisotope. Then we'd biopsy the normal liver and we would biopsy the tumor. Well, when we biopsied the normal liver, we got an 80/20 split between the isotopes from the portal vein and the hepatic artery. When we biopsied the tumor, we got almost nothing but the hepatic artery isotope in there. So, those are different lines of evidence about that.

Now the other thing is, if you put a drug like 5-FU into the hepatic artery, the liver is the organ in the body that gets rid of this drug 5-FU. So of the stuff that goes in the hepatic artery, only about 10% of it gets out and goes into the system to cause systemic side effects. This means you can really push the dose up very, very high so that the 10% that gets out of the liver would be about the same amount as someone would give you in your arm once a week. Therefore, we can give a lot higher doses into the liver.

We actually have a three-pronged approach when we do hepatic arterial infusion and chemoembolization. So the idea is that we want to do chemoinfusion and first shrink the tumors down. Then, we're going to chemoembolize them, which means we're going to plug off the hepatic artery so they can't get any blood from their chief source of blood supply. If they do, that stuff that we plugged the arteries off with is laced with other chemotherapy agent. So, if they drink from the well, it's poisoned. And the third thing is, we don't want any blood vessels to grow back and re-feed the tumor, because that was the problem with chemoembolization alone. For that, we actually rely on the somatostatin, and you've seen diagrams like this before. Somatostatin has lots of functions that we've described, where it stops the cell from dividing, it stops it from making hormones, it stops the hormones from going out, it gets rid of hormone receptors. Over here is another thing that Dr. Woltering has dealt with a great deal; it's an angiogenesis inhibitor. He's going to talk about that later. It stops blood vessel growth, particularly new blood vessel growth. So we think that it's really important that the patients, when they get chemoinfused and then chemoembolized, are on Sandostatin so that it stops the new blood vessel supply from coming back after a chemoembolization, as well. So, this is our three-pronged approach. Basically, we do a chemoinfusion of putting lots of 5-FU into the hepatic artery for a period of months to shrink the tumors down. Then, we strangle them by chemoembolizing them, by blocking the arteries off with this thick oil called lipiodol that is laced with chemotherapy. Then, we prevent the blood supply from coming back to the tumors by using the antiangiogenesis (or anti-blood vessel growing) properties of the Sandostatin itself.

This is the protocol that we've developed. Basically, the patient gets admitted to the hospital four times on a monthly basis. It's not written in stone; we'll skip treatment times for Christmas and holidays, birthdays, and the like. In the first month, we'll put 2 g of 5-FU through the hepatic artery each day for 5 days so the patient gets 10 g. By giving the drug 24 hours a day for 5 days, we get around the chronotherapy problem. During a 5 day continuous infusion, it is 20 times more likely that we'll see a carcinoid cell divide during that time period than during a 6 hour period after an IV injection. It doesn't matter what time of day or night that cell divides because at that very moment we will have a huge amount of 5-FU in the hepatic arteries going to those cells. We are much more likely to poison the dividing cells in this way. Then we let them go home for a month, they come back for the second month, and we do that again. Then they come back in the third month, and the left lobe is the smaller lobe, as you've learned, and there's usually is not as much disease on the left side, so at the end of the third cycle, we'll plug off that left hepatic artery with chemoembolization. Then, the patient goes home and comes back in the fourth month. Then, they'll get another 2 g of 5-FU this time all going up the right hepatic artery to the right lobe because the left lobe has been

closed off. Then we plug off the right lobe. So, in the course of four months you get 40 g of 5-FU straight into the liver, straight into the tumors. If you give it IV, it would take you nearly a year to get that much 5-FU into your body, but it would go all over your body. Your liver is only 8% of your body volume, so only 8% is in the liver. But that's split 20/80 between the artery and the vein. So, 1.6% of the 5-FU you'd get systemically is in the right place at the right time. We, obviously, can increase that dramatically with direct infusion.

Now I don't do this for everybody. Some patients come in and say, "Dr. Pommier, I've got a liver tumor. I want you to do this treatment". But this is risky, and so we have to have specific indications. We've treated well over 100 patients at OHSU. Only one patient has died of a complication of this. So, the indications are that you've got to have new lesions in the liver that appear while receiving Sandostatin therapy. Sometimes we will take the patient off Sandostatin for a period of time and give it back to them to see if they respond all over again. We can try increasing the Sandostatin doses, etc. But, if we're convinced that the tumor has escaped control, we will consider doing this therapy. Another indication is progression of existing lesions while on Sandostatin therapy. So, you've got tumors, they've been under control, but now they're suddenly doubling in size. Or, if we get carcinoid symptoms that cannot respond to the maximal doses of Sandostatin and you're just miserable with the syndrome and we can't control it with any degree of Sandostatin, then we'll do this. We actually get very good symptomatic relief, as well.

There are two ways we can give this to you. We can put a catheter in your groin much like a patient who is going to have a heart angiogram to check their coronary arteries. They can stick the femoral artery, thread a catheter in it, run it up the aorta, out the hepatic artery, and leave it right where we want it below the two branching right and left hepatic arteries so that the chemo will go up both. This is a little problematic. It requires the patient to lie flat in bed with this catheter in their groin. You can't get up and walk around with this thing coming out of your groin or you could kink off the blood supply to your leg and lose a leg. So, you really have to lie flat in bed for about 5 days for each of the four monthly treatments. It's a long time in bed. If you're having diarrhea, the bedpan portion of this is not fun. The other thing we can do is we can do an operation to put a catheter into the hepatic artery for you, and connect it to a thing called a port that we implant underneath your skin on your rib cage. Then, we just stick a needle through your skin into that port and have instant access to the hepatic artery, and we can run the drugs in. When we're done doing it, we just pull the needle out, flush the catheter, and you can go home for a month. Patients, while they're doing this, can actually walk around the hospital. They can go outside. I've wanted to give this therapy to patients at home, but it's almost impossible to find an IV home health service that will give these doses of 5-FU. They'll go home and give someone 750 mg once a week, but not 2 g a day for 5 days. They'll say, "Dr. Pommier, that's lethal. We want no part of this." Even though we've done this many, many times and it's not lethal because the liver gets rid of it, they just won't touch it.

This [slide] is a diagram of this: here's the liver, here's the hepatic artery, and there's a little branch here going to the duodenum that you don't need, so we just cut if off. There's a catheter that goes there and a little port up here. So, this is a patient. There's the gallbladder, the liver is up here, and that's the little artery that you don't need. I just cut it off and put this catheter tip in here, and tie it down with a whole bunch of sutures. It goes to this thing that is a port. A lot of people know what MediPorts look like; you get them for chemotherapy for breast cancer and things up here on the chest underneath your collarbone. But what we do is we put it underneath the skin on the ribcage. You don't need that big of an incision. This is actually someone where I thought I could go in and take all the liver tumors out. When I got in there, there were just too many. So that's a liver resection incision, not a hepatic artery port incision. This was sort of the backup plan. But that's the port underneath the skin. You just stick the needle in there and you've got access to the hepatic artery. This therapy can work dramatically.

This [slide] is a 28-year-old woman from Utah with a CT scan showing her liver riddled with metastases and that her liver is twice normal size. They're all over the place. Here is another cut showing almost complete replacement of the liver with carcinoid tumor. She was basically told that there was nothing to be done for her, just go home and die. So she contacted us, and I said that we were going to treat her. So, we infused her for 4 monthly treatments and chemoembolized her. She went through the protocol. That's her liver after the treatment. It's almost completely normal; there are still little spots here and there, but nothing like what we started with. Her liver is much, much

reduced in size, back down to normal size. There's been dramatic regeneration of the normal liver. This CT scan almost looks normal again. So, the response is very, very dramatic.

When it comes to a biochemical response, showing that your 5-HIAA, your serotonin, your chromogranin A and all the markers go down, essentially we see that in everybody that we treat. When it comes to symptoms, if patients were having bad symptoms and we treat them, essentially everybody gets relief of their symptoms. Objective tumor response where the tumors shrink by more than 50%, it happens in 80% of cases. Complete response where we can't see the tumors on the CT scan anymore happens in about 30% of patients. Now, I think that the tumors are still there. If we do an OctreoScan, that tells all. There is still a little warm glow in the liver saying there's stuff alive in there. But, we can't see it on the CT scan so we call it a complete response. We think that, as time has gone by, we've pushed back the survival for carcinoid patients farther and farther. We started out with that study from the Mayo Clinic showing 17% of patients with liver tumors make it 5 years. With octreotide, we have 67% of patients making it 5 years. This is a survival curve for patients we've treated with chemoinfusion and chemeoembolization protocol: 60% of patients making it 15 years with liver tumors. So, that's a considerable amount of time and that's why we have patients who have made it a long, long time.

Well, eventually those stars that got into red giants exhaust their fuel supply and blow up. They just detonate in the sky. This is the Crab Nebula which is a star that blew up in 1054 AD. Curiously, it was recorded by the American Indians and the Chinese, but in Europe, where we believed the heavens were fixed and perfect, nobody saw that supernova even though it was visible in broad daylight. It's called denial. Here is a star that blew up and made a nice little smoke ring. Here is a star in the middle of a gas cloud that it belched out as it died. This gas cloud is called the Dumbbell Nebula. The amazing thing is, this stuff starts the cycle all over again. These shock waves which are absolutely supersonic go across the galaxy and they hit other clouds of gas, those nebulae that I showed you, and start them collapsing so that stars are born all over again. Those clouds which are pure hydrogen get laced with contamination from the exploding stars. It is those contaminants that made up Earth's heavy elements, and everything we have in life. It turns out that all the other elements on the periodic table except hydrogen, helium and a little bit of lithium get made during those fleeting moments when a star blows up. So every hemoglobin molecule in your red blood cells contains an iron atom that came from the core of a star that blew up. Every phosphorus atom in your bones and in your DNA, every calcium atom in your bones, that's where this stuff came from. So, it's true what it says in the bible that man is made of dust. What it doesn't tell you is that it's stardust.

I'm going to finish up with radiofrequency ablation (RFA). This is a hot, popular technique. It's pretty gimmicky, is the thing I want to warn you about. I think the indications are being overextended and I think the selection of patients should be a little bit better. Here's how radiofrequency ablation works. Once again, we want to use this for a limited number of fairly peripheral tumors. Now, this is my wedge resection slide, as you recall. No, I wouldn't do radiofrequency ablation on these types of tumors, I'd wedge them out. But this is how it works: you have this probe with a handle that's hooked up with a wire to a box that generates radio waves. You stick this into the tumor, and you frequently have to go through normal liver to get to the tumor. We can do this with an ultrasound probe put on the liver at the time of operation, see the tumor, and actually watch our probe shish kabob the tumor. Then, you turn on the radio and it heats up the tip to superhigh temperatures, and basically cooks that tumor and leaves it as charcoal. Then, you stick it in another tumor, turn on the radio, heat it up, and make it into charcoal. Then, stick it into the last tumor, heat it up, make it into charcoal. And when you're done, you've got liver that doesn't have tumors but has three little charcoal briquettes. Now, I really want to compare and contrast the hepatic arterial infusion and chemoembolization protocol with the radiofrequency ablation because there are limitations. The probe will only cook for a distance out of about 2-3 cm from the tip. So, you need to keep the tumor diameter down to a maximum of 5 cm to get a margin of 1 cm in all directions around a tumor, whereas with hepatic arterial infusion, you saw the size of those liver lesions in that young woman. There were tumors that were of all different sizes, baseballs and cantaloupes in there, and they still responded. So, RFA has size limits. Chemoinfusion/chemoembolization has no size limits. Number of lesions: because we go through the normal liver and some of these are in bad places, you can only shish kabob your liver so many times before you cause more damage than good. So, we will do this for approximately five lesions maximum, whereas you could also see on that young woman's CT scan there is no limit to the number of lesions to which we can do the hepatic arterial infusion and

chemoembolization. Lastly, the proximity of a tumor to blood vessels is a problem because as it turns out, your body doesn't want to be superheated or even supercooled. So, as we turn up the heat on this probe, if there are blood vessels near the tumor, they dramatically dilate, increase the blood flow and act as a radiator system to carry away the excess heat. You can keep cooking and keep cooking, and all you're doing is sort of warming up your blood, and the tumor doesn't ever get the "kill" temperature that we want on the part that's near the blood vessel. Whereas, with hepatic arterial infusion, proximity to blood vessels is good because that's how the drug gets in and how we strangle them off. So, these are the comparisons and contrasts. This is why, for most things, I think chemoinfusion and chemoembolization is superior.

These are my criteria for radiofrequency ablation. First of all, the lesion or lesions need to be unresectable. If they're resectable, we should go take them out rather than do RFA. Sometimes, though, patients have atherosclerosis of their aorta, and I can't get a catheter up under their liver. Or, I put a catheter up there once and we clotted if off from the catheter sitting there and I can't get back in. Well, I can't do my treatment of hepatic arterial infusion and chemoembolization for that, so I'll go in and we can consider cooking it with RFA. If a patient has had a successful liver resection but the tumor comes back in the liver and we can't do another resection, and I've already tied off the arteries to one side, then this is a good way to deal with that. Some patients have been treated with the hepatic arterial infusion and chemoembolization and their tumors grow back years later. The first thing I'll do then is get another angiogram and see if the arteries are open again, despite the Sandostatin therapy. If they are, I just re-embolize them. But in some patients, the arteries are permanently shut off, they're not open, that's not the problem, and I can't retreat them with the hepatic arterial infusion and chemoembolization. So, we can use the probe to cook them. Some patients just don't have good livers. They may already have cirrhosis from hepatitis or alcohol history, other liver disease, and I'm really afraid to do a chemoembolization or a liver resection on those types of people because they just don't have the hepatic reserve to pull through that. Or any other serious health problem. A patient may have a great lesion that would be amenable to a liver resection, but they have very serious health problems. They may be too old, too diabetic, have too much heart disease, or they're anticoagulated and it's just too risky. In those cases, we can do RFA instead.