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Transcript
Living-Donor Liver Transplant for Patients with Liver Cancer
October 20, 2021

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Dr. Hughes: Well, thank you very much, it's a pleasure to be here today. I'm going to talk about living-donor liver transplantation and the advantages that it provides us for treating patients with advanced cancers like cholangiocarcinoma and isolated liver mets from colorectal cancer. Our program is a bit unique in this country in that we do a very large number of living-donor liver transplants. In fact, we're the only transplant center that does more living-donor liver transplants than deceased donor liver transplants. And that's because we're trying to find ways to be able to get our patients transplanted. You know, about 14,000 people are on the waiting list. About 8,000 will get transplanted this year, somewhere around 2000 patients on the waiting list will die waiting. And so living-donor liver transplantation is a great way to try to increase the number of people being transplanted. And also, as I said, provide some advantages for treating patients with advanced cancers as you're going to see.

Now, just to reiterate the point of the uniqueness of our program, if you look at the 2020 data of the top volume centers in the country, UPMC looks very different than the others in that we did more living-donor liver transplants than deceased donor. And every transplant center in the country must maintain excellent results, and across the nation now one-year patient survival, which is one of the primary metrics that's used by UNOS to follow transplant centers, one-year patient survival is now up in the 90-percentage range. And so that means we must do an excellent job to be able to perform as we're expected to. And that means that if we're going to transplant patients with advanced cancers, we must be sure that we're doing a good job and we have good patient selection. But I think living-donor liver transplantation allows us to take on certain risks - certain high-risk cases that we may not otherwise be able to because living-donor liver transplantation allows us to plan ahead and schedule a transplant. And that provides some advantages when dealing with patients with cancer.

I'd like to teach a bit about living-donor liver transplantation as part of this lecture, not just about treating patients with cancer, but the actual procedure itself and some recognition of

anatomy, because I think that's important in understanding not only the cancer patient but how the transplant is done. I think it will help clear up some questions you may have as to how we can even do a living-donor transplant. And I'm going to look at - I've pictures that I actually drew myself, some of them on computer, some of them with actually colored pencils. So I'm glad this is my webinar I can't see the audience laughing. But these are my pictures that

I've drawn mainly to point out some specific aspects of anatomy and surgery that might be helpful to help you understand some of the procedure that we do.

And so this is a liver. Looking at it front on is if a patient were standing in front of you. And a lot of people look at the liver and they think that we're the falciform ligament is that that's where the division of the liver is between right and left. And I'll explain what the falciform ligament is. It's an important thing, but it doesn't divide the liver. Actually, what divides the liver is something called Cantlie's line. A Scottish surgeon named James Cantlie realized that the actual division between the right and the left sides of the liver is a line drawn from the gallbladder fossa to the vena cava posteriorly. And this is where all the branching takes place of all the major structures to be able to give an isolated left and isolated right liver that you could either resect or use for transplant or whatever. Cantlie's line.

The real dividing line for the liver along that Cantlie's line, if you look inside the liver is the middle hepatic vein, and the middle hepatic vein is actually part of the left lobe. It's more associated with the left lobe, but it has a couple of branches coming over from the right lobe, particularly from the front of the liver. And this middle hepatic vein drains these areas shown, drains the blood that's in the liver back out of the liver to get to the vena cava and then back up to the heart. And so this middle hepatic vein is an important marker for the division between the right side of the liver and the left side of the liver.

The right hepatic vein is the main vein that drains the right side of the liver, particularly the back part of the right side. And that vein where it sits anatomically divides the liver into two parts, an anterior part, and a posterior part. Those are called sectors. And so that's the right hepatic vein. The left hepatic vein similarly divides the left side of the liver. And so you can see that the planes of the hepatic veins divide the liver in a certain way.

Now, you remember I told you about that falciform ligament. What that falciform ligament is that was coming over into that left side of the liver on that first picture that I showed you, that ligament is actually the closed-off umbilical vein. And when a fetus is in development, this is not a ligament. It's actually a vein that's open and carrying blood. And the blood is coming from the oxygenated blood from the placenta is coming to the umbilicus. The umbilical vein carries that blood through the liver, and I've simplified it here, but it goes to the left portal

vein to the ductus venosus into the left hepatic vein to get back to the vena cava. And that's how oxygenated blood is provided to the fetus during development, and after birth, this vein closes off and becomes a ligament. When someone gets cirrhosis and they get portal hypertension, this is one of the areas where blood actually starts to flow again. This vein will open up and blood will flow backwards through this vein to decompress the portal hypertension. But in the normal state, this becomes a ligament.

Now, the portal vein that carries most of the blood into the liver, about 67 or so percent, about two-thirds of the flow to the liver comes into it through the portal vein, and the portal vein comes in on a different plane. It comes into the liver on a horizontal plane. So you had the hepatic veins that were vertical planes and the portal vein that's on a horizontal plane. And that horizontal plane of the portal vein further divides the liver. And that's what gives rise to what's called the Couinaud segments of the liver. And so Claude Couinaud was a French anatomist who determined that each of these segments of the liver could potentially survive independently because they have all the necessary blood flow components.

And so the segments of the liver are divided by the planes of the portal vein or defined by the planes of the portal vein and the planes of the hepatic vein. And you'll see this in a lot of radiologists' reports and surgeons' operative notes about where certain tumors are, for instance. So you'll see a radiologist report that says there's a two-centimeter mass in segment eight. Well, now you know where that is. Segment eight is the right side of the liver, and it's in front of the right hepatic vein and it's above the portal vein.

The portal vein is really important, not only because it carries a lot of blood flow to the liver, but it also explains why something like colon cancer will metastasize to the liver because the portal vein is made up of the veins that drain into it. So there's the splenic vein from the spleen. There's the inferior mesenteric vein from the primarily the left colon and the rectum, and

the superior mesenteric vein from the small bowel and the right colon. So the veins from those organs drain into these veins that drain into the portal vein that then go up into the liver. So hematogenous spread, for instance, from colon cancer is going to come via this route and get trapped in the liver. And that's why we can get isolated metastasis of colon cancer to the liver.

Now, in further defining anatomy of the liver, there's the artery, the hepatic artery, and it's pretty simple, it follows the portal vein anatomy. Wherever the portal veins go, that's where the hepatic artery goes. And the same thing is true of the bile duct. The bile duct anatomy is pretty much defined by the portal vein anatomy, and so wherever the portal vein and hepatic artery go, that's where the bile duct goes. And on this drawing, just because we're going to talk about this, you can see that initial bifurcation, of course, I've truncated these. The bile duct will be coming up into the liver. But where it divides there, that first division, that's called the hilar area of the bile duct. And it's the area that most commonly we see cholangiocarcinoma, carcinomas of the bile duct. We're going to talk about that.

So that anatomy that's following the portal vein, that hepatic artery, bile duct, portal vein running together even continues all the way out into the microscopic periphery of the liver. And so if you look at a histology slide of the liver like in this figure on the left, you'll see all of these hepatocytes, the main cells of the liver, the ones that do all the filtering of the blood and cleaning of the blood as the blood filters through the liver. You'll see all of those around what's called a portal triad. And the portal triad is the portal vein and the hepatic artery and the bile duct that are all traveling together. And if you look at the top right figure, you can see that portal triad in the left bottom corner. And then the blood trickles through the sinusoids, which are the spaces between the hepatocytes to get to that space on the top right of that figure, which is the central vein. And the central vein is by itself. There's no artery or bile duct around it. It's just a vein. But that vein connects to another central vein and connects and connects until they form the hepatic veins that carry the blood out of the liver. And so that's how the blood filters through, gets out - and gets out of the liver.

It would make sense, then, that if most of the cells of the liver are hepatocytes, then that's what then probably the number one tumor is going to be from the liver. If one of those starts growing out of control, which is basically what a cancer cell is, it's going to come from a

hepatocyte. And that's why there's so - such a high percentage of hepatocellular carcinoma as a primary type of liver tumor. The cells of the bile duct are what make up the majority of the rest of the type of tumors primary tumors of the liver because those come from the cells that line the bile ducts called Cholangiocytes, and they make up about 15% of liver tumors. The other small percentage of liver tumors are the other things in the liver, which are primarily the vessels like the portal vein in the hepatic artery. Those give rise to things like Angiosarcoma and

Hemangioendotheliomas. Those are very rare tumors that evolve basically from the vessels in the liver.

Now, to talk about Cholangiocellular or cholangiocarcinoma, we have to look at the Cholangiocytes and this is an electron microscopy of bile duct showing the Cholangiocytes lining the bile duct. You can even see each one of them has a little cilium, a little hair-like structure on the inside, you can see. And so these line all the bile ducts of the liver. And the types of tumors that can form anywhere along the bile duct are defined by where in the bile duct they are. Are they intrahepatic, up inside the liver? Are they perihilar around that initial branching area? Which even though shown in this picture, looks like it's in the liver, that's actually just outside the bottom of the liver. These hilar cholangiocarcinomas.

And then below the gallbladder are the distal bile duct cancers. Those are the ones that are in the part of the bile duct that goes through the pancreas to the duodenum. And those, you know, if you get a cancer in the lower part of a bile duct that requires a Whipple procedure to remove that part of the pancreas and duodenum and bile duct altogether because they share a blood supply in that region. So you can't just take out the bile duct by itself to remove a distal tumor. Now, most of the tumors are hilar. About two-thirds of cholangiocarcinoma has come from the hilum, right at that bifurcation. A little bit later, I'll explain why that might be, but most of the tumors form there at that bifurcation.

And so where the tumours are is a little bit different in how they appear on X-rays. For example, the intrahepatic ones - intrahepatic cholangiocarcinoma that forms up in the liver usually forms a mass, and it's very hyper-enhanced around the outside, it's less enhanced in the middle. It has a characteristic appearance, and they form as a mass, and that just keeps expanding as it grows. The hilar cholangiocarcinoma is the one near that bifurcation of the bile duct. Those usually don't form a mass. They form tumor inside the wall of that bile duct and

kind of infiltrate along the wall and grow into where you get strictures so that if we do a choloangiogram and look at it, we see a stricture at the hilum. And then the distal ones can also form a mass or a stricture, either one.

So talking about hilar cholangiocarcinoma, this is a pathology picture of a cholangiocarcinoma of the hilum, sled[?] open so that you can see the inside of the bile duct. It

really doesn't look anything remarkable. So looking at it doesn't really help to see that there's a cancer there. And that's the problem with hilar cholangiocarcinoma. It's a very difficult diagnosis to confirm. You can suspect it, but it's hard to confirm it. And so in order to confirm that somebody has a hilar cholangiocarcinoma, we have to do a number of studies and put as much information together as we can and then decide if we really think this is cholangiocarcinoma or not.

One thing that we don't want to do in the case of hilar cholangiocarcinoma is try to do a biopsy of it, like put a needle in it or try to take a segment of it, because that could potentially spill tumor cells. And remember, this is outside the liver. So if the tumor cell spills from a biopsy like a percutaneous biopsy from this region, it's going to mean that they're spread outside the liver.

And so we have to diagnose hilar cholangiocarcinoma in a different way. One thing that helps is by checking a serum CA 19-9 level. CA 19-9 is a tumor marker for cholangiocarcinoma and pancreatic adenocarcinoma. And there was a study done about ten years ago that showed - and they had 129 as a cutoff. If you were above that, your CA 19-9 was above that, that was one piece of information that you could use to increase your suspicion that this stricture at that hilum is actually a cholangiocarcinoma. The next thing we can do is by doing an ERCP and putting an endoscope down and running a brush up inside the duct and trying to brush off some of the cells to see if we can get a diagnosis of cancer, based on what those cells look like.

But here's what those cells look like. It's a clump of cells that the cytologists will see, and they'll have to figure out, okay, do these nuclei look different enough and look abnormal enough that we can call this cancer? And so it's rare that you get a firm diagnosis off brushings where the pathologists will say, yeah, this is carcinoma. It's more common that they'll say these are

atypical cells or these are suspicious cells because of the amount of atypia within the cell. But even still, seeing these cells doesn't really confirm a diagnosis.

Another test that we do is called FISH or fluorescence in situ hybridization, and basically what we're looking for in this type of test is those cells that we did the brushings on, how much genetic atypia is there. And so, you know, a cell that's a cancer cell is going to increase its production of genetic material, it's going to copy genes out of control. And so if you pick four

genes like you see on the left, each of these is a gene that has a different color. They'll look for - to see if a cell is normal based on does it have two copies of each gene like it's supposed to like you see in that left picture that says disomy? Or are there more copies of the gene suggesting that this cell is producing its genetic material out of control? And so like the one that says tetrasomy, there's four copies of each gene that shouldn't be there, or polysomy, where there's even five copies of the gene in red. That polysomy can increase our suspicion that there is actually a cancer at the hilum.

And as it turns out, if you start adding these things altogether, polysomy and the ERCP Cytology, Brushing and the CA 19-9, you can start to put together a good case as to whether someone has cholangiocarcinoma or not. And here at UPMC, we have a test called BiliSeq which actually looks for tumor oncogenes inside the cells that we do brush things on. And we found that there are tumor genes which are - which can increase our suspicion of whether or not those cells are cancerous. And it's important diagnosis to make because the outcome of someone with cholangiocarcinoma is not good. This is a graph from a paper that was done about 20 years ago, showing what happens when either you don't operate on someone in green or you operate on them. And all you can do is place a stent or you operate on them and they have a positive margin. But even if you operate on them and they have a negative margin, their overall survival is not good with just pure resection.

And so in the late 80s and 90s, the idea was, well, can we just take all of these patients and just transplant them without doing any kind of preoperative neoadjuvant therapy, without doing any radiation or anything like that. We're just going to go and transplant these patients. And through the Cincinnati Transplant Tumor Registry database, which basically collects a lot of data from around the country, they found that their survival rates, if you just Willy Nilly transplant someone with a cholangiocarcinoma, their survival rates are not good. So the University of

Nebraska said, well, what if we can irradiate the hilum, and then we can take those people to transplant? When they did that, they actually improve survival, when they did preoperative radiation.

And Mayo Clinic said, well, maybe we can improve on that, and rather than just irradiating people before the transplant, maybe if we started chemotherapy and we gave them 5FU and capecitabine and did external beam radiation, maybe we could even improve our

results further. And indeed, if you select patients according to their selection, which I'm going to show you how that works, and you give them chemotherapy and radiation pre-transplant, you can really improve survival. And they had five-year survivals of around 80%, which was remarkable given what the previous studies had shown.

And so what we have today for evaluating these patients and getting them to transplant, it's a pretty long approval process. First, you have to make the diagnosis or the best diagnosis that you can, that the person has cholangiocarcinoma and then you present them to your transplant committee to say, yes, we think this is a good candidate to go through the protocol. And we do chemotherapy and radiation for six weeks, and at the end of that six weeks, before they can be listed for transplant, we - they have to go through a surgical exploration. They have to be operated on to look to see if there is any disease outside the liver. And if there is, then they're not a candidate for transplant, and if there's not, then they can be listed for transplant. And once they're listed for transplant, then they need to go through a period of waiting.

And UNOS will give them some extra MELD points to get them higher up the list. And so the score that they give them is what's called the median MELD at transplant minus three. So every area of the country is assigned or is told what their median MELD at transplant is. What is the median MELD score that people are being transplanted in your region? So for us here in Pittsburgh for a blood type O it's about 30. So that's where most people with a blood type O are transplanted at a MELD of 30. So UNOS would say, okay, then we'll give this person with cholangiocarcinoma a MELD score of 27 to get them higher up the list. It doesn't get them to the top of the list. It means that if they're going to get a liver at 27, at a MELD score of 27, it means that that liver is likely going to be offered to people higher on the list and declined, until it gets down to a person with this MELD of 27 and we say, okay, well, we'll accept

it for this person, for this patient. So it's likely that the liver is going to be more marginal if you're waiting for a deceased donor.

And so going back to the surgical exploration, so we've determined that this person has got cholangiocarcinoma, we've given them chemotherapy and radiation, at the time of the exploration before the transplant, we have to look for peritoneal disease, which might look like this, [inaudible] implants in the peritoneum. We have to make sure there's none of that. And then we look in the hilum - and remember for a hilar cholangiocarcinoma, there's tumor up here

in the hilum, so we don't want to do anything with that. We're not there to biopsy that or confirm the diagnosis or anything like that. This exploration is to make sure that we don't see tumor cells outside the liver because if we transplant a patient and there're tumor cells outside the liver and now we are going to immunosuppress them to prevent rejection, now we lose their - even their own innate ability to fight cancers and the potential for it to spread very rapidly is increased.

We also look at the lymph nodes in the hilum, and we take out two lymph nodes, the one by the artery and one of the one by the bile duct, and we send those to the pathologist and they do frozen section analysis and they say if there's tumor in those or not. We would like to be able to take a section of the bile duct and send that to the pathologist. But if we're going to - if we're just here doing an exploration and we don't have a donor right here ready to go and we're not going to transplant this person in this same exploration, we don't want to be cutting out part of the bile duct because we would have to reconstruct that. And if there's cancer there, then we'd be trying to reconstruct a cancerous bile duct. And so we're not able to look at extension of the bile duct to that initial surgical exploration.

But if we go through all of those processes and the patient ultimately gets transplanted, the most recent data here, this is from 2020 shows that ten-year survival rates in these patients is actually really good. But this is a long process of selection basically. Probably one patient out of six or seven actually makes it all the way through this protocol to get approved for transplant and actually gets their transplant.

So here's a patient that came through - came to us looking for potential transplant. 40 years old. He's got primary sclerosing cholangitis in which he's got strictures all throughout the

liver, making it even harder to diagnose a patient with PSC. And the ERCP showed a stricture in that hilum, and he had some stents placed just to keep it open. We did the cytology with the brushings, and we did not see specifically malignant cells. They were some inflammation, but no malignant cells. The FISH was positive. He did have polysomy. So that was suggesting that he had cholangiocarcinoma. But his CA 19-9 was not real high. So we have some data to help us and some not. His images really don't show anything other than the fact that he's got some inflammation, this dark area in the liver on the left. And on the right, you can see these lines coming out from the center. Those are actually dilated bile ducts because of his stricture.

And so our process being able to offer living-donor liver transplant makes this a little bit easier for the patient. So we have cholangiocarcinoma suspected and so we're going to treat him as though he has it. He has chemotherapy and radiation like he's supposed to. He goes to our committee, we say, yes, he's a candidate and he has a living-donor, someone who wants to donate to him. So we evaluate the donor while he's going through his chemotherapy and radiation and we have the donor ready to go. And on the day of his surgical exploration, we bring him and his donor into the hospital and we take the recipient to the operating room to do his exploration. But we don't bring the donor to the operating room yet. Normally we bring them into the room - at their adjacent rooms at the same time when we have a living-donor procedure.

So we explore the recipient first, and if we see no evidence of extrahepatic disease, then we can bring the donor right into the operating room next door and we can start doing a donor procurement and we can move straight to transplant. We don't have to close the patient, wait for him to recover. We put him on the waiting list, wait to get a deceased donor, and then transplant him sometime down the road. And so in this patient, we did our exploration. We checked that hepatic artery lymph node, it was negative. We checked the bile duct lymph node, it was negative. And we did a section of the bile duct, which we can do since we're going to transplant this patient, and it was positive. And we did another section, and it was positive. And we were getting down the bile duct and we couldn't get a positive margin, which means that the only way to clear the bile duct is to do a Whipple in addition to our transplant.

And so that's what we did. And so to do a Whipple, we had to take out part of the pancreas, the distal part of the stomach, the proximal jejunum and duodenum, and the liver. And that left us with a big hole along with the area where we had taken the Whipple specimen

out. And so this is an operation, the liver used to be in this space. And I'll point out some structures. Right there as the vena cava, that sort of purplish area that I highlighted in the back. You can see the pancreas, we've divided in half is right there. This vein is a superior mesenteric vein coming from the small bowel and the colon. This is the splenic vein that's behind the pancreas. You can't see it, but that's the splenic vein. And really hard to see back there is the hepatic artery. And so we had to reconstruct all of this from this large space.

This is what the donor gave us. And if you remember those pictures I showed you at the beginning of the anatomy, we've got the right hepatic vein, which we've divided in the back. We've got those two little veins in the front of the liver on the cut surface, which had been going to the middle hepatic vein. We're going to have to reconstruct those. And then we've got the portal vein artery and bile duct down below. So we reconstruct the outflow first, the hepatic veins first. And so we use a piece of vein, and I'll show you where we get this vein from. But we use a piece of vein to make the right hepatic vein bigger so that it has a much larger outflow site so that we don't get a stricture at the outflow site because venous outflow is really important in a living-donor transplant. And we sew that right hepatic vein to the side of the vena cava in a great big patch.

So now we have to get outflow from those two veins in the front. And remember here, I'll show you this little diagram up there in the top right. So we have those two veins on the cut surface and remember those segments. So one of these veins is a segment five vein and one is a segment eight vein, and we need to reconstruct those. And so where we get the vein from to reconstruct those is a deceased donor. Anytime somebody dies and donates their organs, they'll also donate their blood vessels, their iliac artery, and veins. And we can keep those in storage and be able to use those in people who are having living-donor liver transplants. So most of these patients have two donors, a living-donor - liver donor and a vein donor.

And that iliac vein, common iliac with internal branch and external branch is perfect to reanastomose[?] Those two veins from the front side, the anterior side of the liver, the segment five and eight veins. Which is then reanastomosed to the stump of where the middle and left hepatic vein used to be from the original liver. And then we reconstructed all the portal vein, artery, you'll see a little bit more about that in the bowel to reconstruct all of those components.

And then he has a bile drain. We leave little stents into the bile ducts while they heal. We'll disconnect that drain after day one and just leave the little tube under a piece of tape for about six weeks and take it out in about six weeks. And if we want to [inaudible] the cholangiogram we can [inaudible] in that tube up into the bile duct, and you can see where the bile duct joins the bowel at that anastomosis.

And that operation took us about six and a half hours, but he didn't require any blood transfusion. The explant pathology, sure enough, he did have cholangiocarcinoma. There was

no lymphatic invasion. The lymph nodes were negative. This is the specimen. From there, you can see a tinny - that white areas that opened up bile duct, that little, tiny hole in there is where his stricture was. Sorry about that. And here's the Whipple specimen with part of the pancreas, the duodenum is transversely at the bottom, and the bile duct is coming into it. And the cancer had gone about halfway down this duct, but all of the margins were negative. This is him about four years - almost four years. December will be his four-year birthday for his new liver, and he has no evidence of recurrence.

Now that's hilar cholangiocarcinoma. Now, what about the intrahepatic cholangiocarcinomas, the ones up inside the liver? And why are they different? Well, the reason they're different is because in fetal development, the bile ducts from inside the liver versus the bile ducts from outside the liver come from two different places in the fetus. And then they fuse, and they fuse at the hilum. So it - you kind of wonder is, is that fusion site part of the reason why cancers are so common to form at that bifurcation in the hilum. But looking at cholangiocarcinoma, there's a recent study of over 500 patients showed that doing any kind of surgical resection on a person with cholangiocarcinoma in the periphery really doesn't yield good results, and most of those people recur.

But it's interesting that most of those who recur, recur only in the liver. So if you took out their left lobe, for instance, for a segment two tumor, they may recur in the right low. But what if we had taken out their entire liver? And as it turns out, a recent paper by Lunsford at Methodist Hospital and MD Anderson showed that there can be excellent survival now with transplantation for patients with intrahepatic cholangiocarcinoma.

And so for our protocol, we know that intrahepatic cholangiocarcinoma, for whatever reason, maybe it's because of those changes in the developing fetus or whatever that those are very aggressive tumors. And so we're more aggressive with our chemotherapy and we also continue it for longer. So they get six months of chemotherapy, not only because that gives them the treatment, but it also gives us time to determine, do they have any tumor outside the liver? Is anything showing up outside the liver? It basically lets us determine what's the biology, and it gives time for something to pop up if it's going to show up outside the liver.

And so we had a patient come to us 65 years old with a four-centimeter mass in segment five, six. You know where that is. It's in the right lobe. And she had an intrahepatic cholangiocarcinoma, and here it is. Remember, this looks a lot like that earlier picture of an intrahepatic cholangio, bright outside, dark in the center. And we put her through the protocol and her son was her donor, and we took her to the operating room and we did what we usually do, which is we explored her first to see if we see any extrahepatic disease and we didn't see any.

And so her son donated right there during that procedure. We took him into the adjacent operating room, and this is the piece of liver that he gave us. It had these three veins on the cut surface, a segment five and two segment eight veins in the front. The right hepatic vein. There were two bile ducts associated with this liver, and we hooked it up. You already know how. We did the right vein with a little patch that we connect. We did the iliac veins to connect all of those to the - to provide the outflow. We connect the portal vein to the portal vein, the hepatic artery to the hepatic artery, and then we connected the bile ducts to the intestine. Now, this is called a Roux-limb or a Roux-en-Y hepaticojejunostomy. Roux from the guy who invented this operation. César Roux, who is actually a Spanish surgeon. Why? Because it looks like a shape of a Y, and hepaticojejunostomy, meaning connecting the hepatic ducts with the jejunum.

And so the way that's done - and sorry, my drawings used a whole liver when I drew this initially, but the principle is the same. We come down the bowel to a point where it's movable. And the reason that we're doing this is because when we divide the bile duct in the living-donor procedure, it's way up high in the liver. Way up at close to the surface of the liver. We don't have any mobility. We don't have the ability to stretch the bile duct to make it meet the old bile

duct. And so especially when we've taken a chunk of the bile duct out as part of their operation for cholangiocarcinoma, you know, we've come down as far as we can to the pancreas.

And so we divide the bowel. We close off one end, and then we make a little hole in that part of the bowel, that's the size of the bile ducts we need to connect it to. And we tunnel a cholangiogram catheter into there to act as a stent, we tunnel it into the bowel and out the hole. And then we connect that. We bring that bowel up and we connect it to the bile duct and we leave that little stent up in the bile duct. And then we come down further and we reanastomose the bowel to the side of the jejunum. And this does two things. Number one, it lets the

peristalsis of the bowel carry the bile from the liver downward away from the liver like we want it to. And it also prevents food from getting into the area where the bile duct is connected to the intestines so that we don't get obstruction from particulate matter.

And so that's what we did. We did this reconstruction on him. And it took us nine and a half hours. But - and we check all the blood flows. I didn't mention that before. We check all the flow and all the blood vessels. He didn't get any blood products and this is his liver at the end. You can see this is the obviously preceding cirrhosis. I'm saying him it's a her. This is the explant pathology showing a five-centimeter Cholangiolar differentiation carcinoma. So this is cholangiocarcinoma. This is that tumor that we saw in the CT scan. This is her 18 months post-transplant. No evidence of recurrence. So that's hilar cholangio and peripheral or intrahepatic cholangiocarcinoma.

Now, real briefly for colorectal cancer. Previous attempts to transplant patients with just taking patients as they come and transplanting them because they've got tumor in the liver were not met with good results. But as we become more selective, the results improve just like happened with cholangiocarcinoma. In fact, a recent international consensus group, this just came out this year, and the important part is the bottom right of this slide, which basically says that if they don't have any tumor outside the liver and they've gone through chemotherapy and radiation, as well as a six month period of observation to see if there's any evidence of extrahepatic disease, that person's a transplant candidate, and that's the protocol that we follow here.

And so we had a patient come to us, who is 66 years old. He had rectal adenocarcinoma that had been removed and that was back in 2016. And so he had been kept on chemotherapy. He had had Y-90 to the whole liver to try to treat these tumors and keep them in the liver and keep them from spreading. And he went for four years before presenting to us for a potential transplant. All that time, never having any evidence of extrahepatic disease. And this is his pre-transplant imaging. He's got multiple tumors, some of them partly necrotic, some of them not.

And so our protocol is that we confirm the diagnosis that he's got, that this is colorectal cancer to liver by reviewing their - these slides had been done from his initial biopsies. We

waited the six months, he got his chemotherapy and all of that had already been done. He got a colonoscopy to make sure there's no evidence of colon recurrence. And he got abdominal and full-body imaging, including PET-CT to make sure that we couldn't identify any extrahepatic disease.

When we did - followed our protocol, we brought the donor in with him. The donor waited while we did an exploration on the recipient to see if there is any tumor outside the liver. We found one little nodule, which was negative. And so we proceeded with transplant. And this is what his donor gave him. And you already know the drill. We connected it just like we connected the other ones. We did a [inaudible] up to the bile duct. Took us 11 hours. We did all the flows. They were good. We didn't lose much blood. And so he didn't require any blood transfusion.

And this is the final diagnosis. He had poorly differentiated carcinoma. Four separate lesions which had been in his liver for the last four years. The margins were negative. We checked for PD-L1 to see if that can direct us in any future need for chemotherapy or immunotherapy. And obviously, in the liver, there was previous radioembolic beads from when he had received Y-90. That was all in his explant. And here's his explant with these large tumors. The largest one was eight centimeters. This is him now two years post-transplant with no evidence of recurrence, so you can see his liver looks very good.

So I'm about out of time, but I hope this is kind of given at least a background of living-donor liver transplantation, how it's done and swayed you a bit into seeing that for selected

patients, and the key there are selected, we have to be very selective about how we choose people for these protocols, we can treat hilar or intrahepatic cholangiocarcinoma and isolated colorectal mets with liver transplantation. And thank you for inviting me today, and I'm happy to answer any questions. And the first question -

Speaker: I'm sorry, I was going to say that I was going to remind the learners that they can post their questions in the chatbox. Thank you.

Dr. Hughes: Yeah, I see one has come up. Is there early detection for cholangiocarcinoma? Not right now. I think there are a number of studies looking at - as we are with the BiliSeq test

looking to see if we can find potential genetic markers for cholangiocarcinoma. Of course, CA 19-9 is a marker as well. But even still, it's not an easy diagnosis to make, and especially not an easy one to make early. I think one of the reasons that people with primary sclerosing cholangitis have a little bit better outcomes than others is because they're usually being followed by their herpetologists or gastroenterologists because of their PSC, and that's why their cholangiocarcinomas may get picked up early.

Risk factors in cholangiocarcinoma. As far as I know, there's no correlation with alcohol use, for instance. So that was another question. Association with primary sclerosing cholangitis is probably the biggest association for cholangiocarcinoma, and that's why we tend to look very closely for it when we see somebody with a dominant hilar stricture.

The typical follow-up - this is the next question, what's the typical follow-up after transplant? It depends on what type of tumor, but basically, we follow serial abdominal imaging - abdominal and chest imaging for about five years. Usually, we do chest and abdominal imaging every six months for the first three years and then year four and year five. And if the tumor markers had been positive pre-transplant, we'll usually follow those post-transplant as well.

Any other questions? Let's see. **Are cysts in the liver any indication of future liver cancer like cysts in the pancreas are?** The cysts in the pancreas that you're talking about are probably IPMNs, which can be precancerous. Cysts in the liver can be benign. In fact, the vast majority are benign, and those can just be observed if there's a cyst that is septated or that

bleeds into it. Those might be ones that we want to either biopsy or resect because there is a cystadenocarcinoma which can form. But like I said, the vast majority of those are benign, and we usually don't do anything for those unless they get so large that they're causing symptoms like compression on the duodenum, that kind of thing.

Will the recipient or donor liver grow back to normal size after the transplant? Well, what allows us to do living-donor liver transplants is the ability for the liver to regenerate. And so that regenerative process occurs both in the donor and the recipient. And so - and it's a fast process. So the right lobe that we take out from the donor is about 60% of the liver. So we leave the actual donor with about 40% and the recipient gets 60%. By the end of eight weeks,

both donor and recipient will have livers that are about 90% complete, meaning 90% of their full size, so that's a lot of growth in that short period of time. And what happens is if you remove the right lobe, you don't grow a new right lobe, you just hypertrophy the left lobe. And that, like I said, that happens very quickly.

Have the outcomes improved for liver donors over the last several years? Yes, I think outcomes have improved. There are still potential complications, particularly biliary complications in donors. There's always a potential of a donor death. There have been six in this country. And three patients - an additional three patients have required transplants themselves. But with the increasing numbers that are being done, just as with any kind of operation, the expertise improves. You do want to be at a center that does this routinely because it is a very highly technical operation. And most of our patients are out of the hospital and about five to six days, most of the donors.

Can anyone refer patients to your transplant center? Yes, you can. We can have self-referrals. We have a website that you can go to and you can self-refer. And so that's an option. Or your physicians can call us as well and can refer you.

If one parent has cholangiocarcinoma, is there a test to check the daughter? No, there's no specific test to look for the potential for cholangiocarcinoma in a relative.

Do the patients who are candidates for a living-donor liver, such as patients with cholangiocarcinoma, usually have high MELD scores? No, they don't. That's actually the

problem. Most of these patients develop cholangiocarcinoma and their MELD score is low. And so that's the problem with trying to get them a liver from the deceased donor list. Now, for hilar cholangiocarcinoma, that's the only one of the three types of tumors that I describe that UNOS will give MELD exception points to. If you have colorectal metastasis to the liver, UNOS will not give you any increased MELD points to move you up the list. The same is true for intrahepatic cholangiocarcinoma. And so that's obviously a disadvantage for those people who need transplants. And that's one of the main reasons why living-donor liver transplant is such a good option for these patients.

Is this more common with cirrhosis patients? Any type of tumor of the liver is more common in a patient with cirrhosis. It's that process of whatever's caused the cirrhosis over a period of time of damage and repair and damage and repair to the liver over years, which is usually what cirrhosis takes to develop, you know, ten to 20 years of whatever process, whether it's alcohol, or hepatitis, or primary sclerosing cholangitis, or any of them, lots of different diagnoses for - that lead to cirrhosis. Those patients may have a much higher incidence, particularly of hepatocellular carcinoma. And then for PSC patients, they're at particular risk for cholangiocarcinoma.

Do people still need chemo then? We're learning that we're giving chemotherapy after the transplant if a patient has the transplant and we identify on the explant pathology an area of the liver where there was a positive margin. For instance, we transplanted a patient that had a positive margin on the portal vein. It's not a commonplace for it to spread, and so we

don't usually check the margin during the operation. We do now. But if we were to find a positive margin or an extra lymph node that had not been taken out at the time of exploration but came out with the explant that had tumor in it, suggesting that there was positive a positive lymph node, then we would consider chemotherapy for those patients post-transplant.

What risk do liver hemangiomas pose? Very little if they're small. Once they get big upwards of 10 centimeters or so, then we start to consider should those be removed, not because of a risk of cancer, but because of a risk of injury or bleed to those.

My mother passed away from pancreatic cancer. They told her at the time the Whipple was not an option. Still don't understand why. What are some reasons a

Whipple cannot be done? Well, number one, we have to make sure the person's an operative candidate. A Whipple procedure by itself is a very big operation. And the same is true for a Whipple as is true for a transplant. If you're going to do a big operation like a Whipple procedure, you want to make sure that there's not going to be tumor left behind. These are operations that we're doing with the intent to cure. So if there's a lymph node positive or something like that, that might preclude them from saying that this person is a candidate for a Whipple.

Has your success been as impressive with neuroendocrine tumors? Yeah, actually - I actually I was going to talk about that in this talk, but then it started running long. So I was like, well, I'll limit it. Neuroendocrine tumor is another tumor that we have a protocol for. And actually, these can be really advanced. And we even transplanted a patient that we knew had a positive lymph node outside the liver. And the reason was that he had been for ten years or more with maintenance of his tumor in a stable state using medications. And there are some new medications, relatively new medications for chemotherapies for neuroendocrine tumor, which are excellent. But this patient, his liver had gotten to the point where he - his liver could not tolerate any more chemotherapy. So without a new liver, he was going to have to come off chemotherapy.

And so we transplanted him about three years ago, and he has done beautifully and has not had any evidence of recurrence since that time. We took that node out, of course, at the time of transplant, but he's had no evidence of recurrence and has done really well.

Any post-transplant immunosuppressive therapy used? Yeah, we have to immunosuppress every person who has a transplant. And so we actually try to switch them to immunosuppressive therapies that are - that have actually some anti-cancer properties too. So most of these we try to get on Everolimus and Cellcept as opposed to Prograf which are a little bit less cancerogenic, so to speak. And so - but all of our patients are in some degree of immunosuppression. We try to limit it as much as possible based on liver function tests. But yes, so we do have to immunosuppress them.

How many live donor centers are there in the USA? Right now, I think there's about - around 30 places in the country that do living-donor liver transplants, but only ten do more than ten. Only ten transplant centers in the country are doing - routinely doing more than ten living-

donors per year. We're doing by far the most. There are a couple of other centers that are doing - we do generally between 90 and 100 per year. There are some other centers that are doing around 30 to 35. And then after that, the numbers get much smaller.

Have you seen an increase in NASH and NAFLD with carcinoma complications versus alcoholic? Well, we're seeing a lot more NASH and NAFLD patients in general coming to us for liver transplant as every transplant center in the country is. And these people have cirrhosis and their cirrhosis that leads to their risk of hepatocellular carcinoma. So we see a lot of - we don't usually see cholangiocarcinomas in these patients, we usually see hepatocellular carcinomas. But yes, they can occur in NASH patients, and we're seeing a very high number of NASH patients coming to see us.

Speaker: Dr. Hughes, we have time for one more question.

Dr. Hughes: Okay. Where do you point recipients who may be having a difficult time finding a donor? That's a great question. And actually, believe it or not, about 15% of the transplants that we'll do this year will be from altruistic donors, people who have no idea who they're donating to. They just saw something on social media or Facebook or whatever it might be and decided that they wanted to donate to them. If you come through our program for a transplant evaluation, if you're someone who needs a transplant, we have a program called the Champion Program, which is an educational program to help recipients understand how to get the word out that they need a transplant.

Most people are scared that they're going to have to go directly to someone and say, Hey, will you give me part of your liver, which is real hard to do? And we know that. And so we recommend getting a champion, which is a person who does that for you, who gets the word out for you. So you're not the one asking. And it goes through a number of different ways, particularly through social media, to get the word out that you need to a liver. And usually, if people know that you need one, you'll be surprised that who will come out as a potential donor. And so most of our donors aren't even related to their recipients. And like I said, about 15% will be altruistic.

Speaker: Thank you, Dr. Hughes, for an excellent presentation, and there were some very good questions.