CHRISTOPHER B. HUGHES: When we were putting together the curriculum for this conference, Dr. Umar said, he said, I want to talk about this great life saving live donor transplant procedure. Chris, why don't you talk about one of the most dreaded diagnoses a patient can have?

Yeah, right after that. I said, sure, boss. So, in putting this talk together about cholangiocarcinoma I mainly wanted to stress a couple of things. Number one, why we treat cholangiocarcinoma the way that we do. And number two, to give you an idea of what these patients and our medical team have to go through to get a person like this to ultimately be transplanted. Because it's probably one of the most labor intensive things that we treat. So cholangiocarcinoma, if you look at all primary liver cancers is about 15% of the total.

Most of them are eight ccs. And then there is a small subset of things like fibrolamelar HCC and some of the angiosarcomas and hemangioendotheliomas, those kind of things. But that's, for cholangiocarcinoma, about 5,000 to 8,000 or so cases per year. 10% to 30% of those patients with PSE will actually develop cholangiocarcinoma at some point. And there are other known risk factors that can lead into somebody getting cholangiocarcinoma. Worldwide, it's things like liver flukes and stuff like that. But there's also some subsets of cholangiocarcinoma that can be associated with hepatitis B and hepatitis C.

You've probably all seen these embryology pictures. Always hated embryology. But it's important in this case to understand the formation of the bile ducts, because I think that helps us understand why some of these bile duct cancers behave the way that they do. And the intrahepatic biliary ducts arise from a different place embryologically than do the extrahepatic biliary ducts.

And so the cranial part of the ventral foregut endoderm forms the intrahepatic ducts. And the caudal part forms the extrahepatic ducts. So the extrahepatic ducts form more early as cholangiocytes. The interhepatic ducts actually form as hepatoblasts first. And then they differentiate into cholangiocytes.

And they form in the liver, those hepatoblasts form next to the portal vein and the sheath along the portal vein, which then those. That a little layer of cells around the portal vein makes cholangiocytes, and then they start to form tubular structures along the portal vein. Those two things fuse at the hilum.

And whether that has something to do with why we see such a high percentage of cancers, cholangiocarcinomas at the hilum, is not really known. But what we do know is that the three parts of the bile duct cancers, intrahepatic, hyler, and extrahepatic down toward the pancreas, respond very differently and are treated very differently for that reason. So there's a lot of transcription factors, genetic factors, that go into the differentiation of the bile ducts. And we're actually using some of these genetic things to now diagnose cholangiocarcinoma and we see abnormalities in the genetic regulation of the biliary system.

So the bioducts, like I said, we have intrahepatic, hilar, and extrahepatic. The peripheral ones, these are the intrahepatic ones. The peripheral ones respond very poorly to any kind of treatment. Those are the ones that formed along that portal vein sheath. If you get a cancer that's intrahepatic, the likelihood that you're going to be cured is very, very small.

The transplant centers in Canada got together and pooled all of their data about incidental cholangiocarcinomas that they found in people after a transplant for something else. So the person had a transplant, the x plant went to pathology. Pathology looked at it and found smaller than one centimeter, one tumor smaller than one centimeter, incidental cholangiocarcinoma and those patients went on to have a 70% recurrence after their transplant for intrahepatic cholangiocarcinoma.

So when we have a protocol for transplanting people with cholangiocarcinoma, if it's intrahepatic, no, nobody transplant those. And UNOS will not allow us to have any extra meld points to transplant someone with a cholangiocarcinoma that is up in the liver. So that's why they're excluded.

The ones on the far right, the extrahepatic biliary tumors that are down below the hilar, the ones where the bile duct goes through the pancreas, obviously those we're not going to worry about liver transplant because those aren't in the liver. Those are people who get a whipple. They get a pancreatic duodenal resection to get the distal bile duct down. So for transplant liver transplant purposes, we're just talking about hilar cholangiocarcinomas. And that happens to be the most common ones.

In the hilar, cholangiocarcinomas have a staging system that's the bismuth staging system. It's 1 through 4, based on where the tumor is, where the tumor cells are. And most of those are resectable types 1, 2, 3A, 3B can be resected without a transplant as long as the rest of the liver is OK. So like for type 1, you can just take out that segment of the bile duct and reconstruct the bile duct. for type 2 same thing.

And for type 3A, you would take out the right lobe and reconstruct the left lobe. 3B, you take out the left load and reconstruct the right lobe. So really, that just leads for transplant purposes unresectable hilar cholangiocarcinoma, ones that we can't resect because we're not leaving any liver for the person to survive on. So that leaves basically the type 4s.

And so somebody asks the question, well, if transplant is a good idea for hilar cholangiocarcinoma, why resect any of it? Why not, no matter where it is in the hilar, just do a transplant on those people and they don't get a survival advantage. And so the data out of Mayo showed that if you can respect them, you should resect them and not try to transplant.

So historically, the treatment of cholangiocarcinoma, the results have pretty much been abysmal, and the idea of transplanting early on when transplant centers started saying, well why don't we start transplanting people with cholangiocarcinoma, the results were also very bad. And so some of the early results had a five year survival rate of 20 or so percent, which really was not acceptable. And so for the most part, historically cholangiocarcinoma has been a contraindication to transplant because the outcomes were so bad.

So the University of Nebraska, in the '90s, actually said, well, why don't we add something to transplant? Why don't we radiate the area where the tumor is first, and then proceed to transplant? And when they did that, they actually saw some improvement in the outcomes, not great, but some improvement.

And so Nebraska kind of started this idea of, what else can we do in addition to transplant? And so Mayo Clinic added on to that and said, well why are we just doing radiation? Why don't we do chemotherapy as well? And so Mayo Clinic came up with a protocol of giving 5-FU which is a radio's radiation sensitizing chemotherapy to try to make the area more sensitive to the radiation treatment that's being given. Why don't we give 5-FU and radiation, external beam radiation, and Mayo actually early on was putting iridium wires up into the bile ducts to irradiate, this brachytherapy, to radiate the bile duct from inside the bile duct.

And the results actually for doing that process, chemotherapy and radiation for six weeks, then under Mayo's protocol, they said, before we transplant these people, let's explore them, look and see if there's any extra hepatic disease. So we'll do an exploration we'll look at lymph nodes. If everything is negative, and we don't see any tumor outside the liver, we'll go ahead and list them and keep them on maintenance chemotherapy until they can get a transplant.

And so, one of the first papers they put out in the early 2000s, they had had 56 patients who came through that they said, OK, we're going to put you through this process. And fewer than half at the end had actually made it to transplant. Because a lot of those either they had tumor at the time of their exploration or we found it in the lymph nodes. We can't transplant you because you're going to recur. Or they got so sick by the time they got to transplant that they just couldn't be transplanted anymore.

Because you can imagine a person with PSC, who already has-- you know, who's cirrhotic and already has, you know, muscle wasting, all the things that people with end stage liver disease have. And now you're giving them six weeks of radiation and chemotherapy and put them through an operation, and then kept them on chemotherapy, getting a person through all that's kind of hard.

UNOS, the United Network for Organ Sharing that oversees transplant for the whole country, has looked at this and said, OK, this is the type of protocol that all centers need to follow. And so in order to get a patient transplanted with cholangiocarcinoma, all centers need to follow this process. And so, some transplant centers will not transplant cholangiocarcinomas because it's very labor intensive. It requires a big team and all that just like Dr. Kumar was talking about the living donor program. Not all centers do that because it's a big investment. These are not easy patients.

And so, but UNOS said, we want everyone to have the same protocol and you have to submit to us, we have to submit to UNOS what our protocol is and prove that we're following it on every patient. So the hardest part actually is the diagnosis, is confirming as much as we can that a person has cholangiocarcinoma. It's not an easy diagnosis to make. And so we have things like, OK, we can check their CA19 9.

OK, and the studies have shown that if a person that we suspect has cholangiocarcinoma, which is usually a person who comes to us with a hilar stricture, and we check a CA 19 9 on them, if it's greater than 129, then there's a 60% chance that really is a cancer. So that's additional information to help you understand that this person really has cholangiocarcinoma. You're not sure yet.

And so, in making the diagnosis you kind of have to understand a little bit about how the tumor can grow. Because it can grow in different ways. Some of these cholangiocarcinomas will form a mass. Some of them don't. If it forms a mass in the hilum with a stricture with elevated CA 19 9, then you're gaining more and more confidence that this person really has cholangiocarcinoma.

But much of what we see, which is a higher association to patients with PSC, which is this periductal infiltrating type of cancer, there may not be a mass. And trying to make the diagnosis of, yes, those are tumor cells there may be difficult. Because part of the problem is with the requirements of UNOS and the original Mayo protocol is that you can't biopsy any of this percutaneously or by EUS. Because if you put a needle into it, the studies have already shown that there's a high risk of tumor seeding and recurrence after you do that.

So if a person comes to us and they had a mass and some center somewhere said, oh, we biopsied it and they have cholangiocarcinoma, we want you to transplant them, we say we can't transplant them now. Sorry. And so the diagnosis has to be made without real good tissue. Now we can do brushings of course with endoscopy, with ERCP.

And we can brush the area. But here's an open bile duct of a person with cholangiocarcinoma, and if you look at the lining of the bile duct it really doesn't look that bad. So what are the chances that we're going to get definitive brushed off cells that say, oh, this is adenocarcinoma. That's usually not what the cytologist is going to read.

They're going to say, oh, these are suspicious these are atypical. And so we're saying, OK, does this person really have cholangiocarcinoma or do they have some atypical inflammatory type cholangiocytes from the brushings because they have PSC, right? But the more that you put the information together, the more you can be confident that the person has cholangiocarcinoma.

And we can do aneuploidy studies. We can do fish studies to look for genetic abnormalities, to look for polysomy essentially. And then we can say, OK, well, if they have polysomy, that's more information. Because obviously they have some genetic abnormality there as a tumor would.

And pretty soon as you put all these things together, the data is coming in your favor that, OK, we've got a CA 19 9 that's high. We have a fish. We have a stricture. We think this person has cholangiocarcinoma even though we don't have it definitively in tissue. Why is it important to, as much as you can, have a definitive diagnosis?

Truthfully, it's because you have to convince the oncologist to give the patient chemotherapy and radiation for six weeks in a person who is not overly healthy. And sometimes the oncologists will stand their ground and say, we want more information, and so you just kind of have to pile up as much information as you can.

Now one of the things that we're doing more recently. And actually. Adam Slifka from GI is leading this, is BiliSeq. And it's a test that we can order as a panel. It's next generation sequencing looking for genetic abnormalities in the brushing cytology that we've done. And basically it's a 28 gene panel.

And some of these genes have been associated with higher incidence of cholangiocarcinoma. So if you see an alteration for instance in the KRAS gene or the TP53 gene, we know that those are highly associated with genetic abnormalities that we see in patients with tumors that are going to carcinoma. And so this is just more stuff that we add on to trying to convince ourselves and the oncologists that this person has cholangiocarcinoma so that we can start the process of getting them treated for it.

So our inclusion criteria for putting a person through our protocol to get them transplanted is that they have a hilar-- unresectable hilar cholangeo, and we've done our diagnosis based on these things that we have that we just discussed. Where they are excluded if they have lymph node involvement or any extrahepatic disease, if their tumor size is greater than three centimeters, they're excluded. If they have a previous attempt at biopsy or resection of a tumor, or if they have intrahepatic meds or peripheral cholangeo, like we talked about before.

And so that basically just leaves us with a hilar tumor that we have enough diagnosis criteria on and that's otherwise unresectable. So at that point they receive 5-FU and radiation. It's done like. It's basically external beam radiation that's given five days a week for six weeks. And they get the 5-FU at the start of that for radiation sensitization.

At the end of that six weeks, they have to be explored. Now, here's where an advantage comes if a person has a living donor. Because UNOS says, you don't get to raise this person-- UNOS will give extra points for a person with cholangiocarcinoma, extra MELD points to get them there to show you what that schedule is. Because it's still a long process to get them to transplant.

But UNOS, like I said, they say we have to we have to do an exploration first to show that the person does not have cancer outside the liver. So basically what we're looking in that operation is peritoneal seeding, which usually just shows up as little dots of cancer spread out, peritoneum, surface of the diaphragm. And the other thing that we look at in that operation are the lymph nodes that are closest to the hilum of the liver.

And that's the periarterial node which is next to the hepatic artery and the pericolodocal node which is next to the bile duct down the pancreas. We take those two nodes out in that exploration. We give it to the pathologist. And if they say there's no tumor there, and we say, OK, we've done what we can do to show that we don't have extrahepatic disease. We've looked outside the liver and we've checked the closest nodes.

Now, if we don't have a living donor, now this person, we close them. They get admitted to the floor. They go through recuperation, get discharged, they're continued on chemotherapy until they get their transplant. If the person came to us with a potential living donor, we could actually include this operation in their transplant.

And so what we've done in this case, in these cases, is, we have the donor ready to go to the operating room, but we take the recipient in first. We do the exploration. We let the pathologists look at the nodes, and if they're negative, we can go ahead with the transplant. There's no wait. Because we don't have to wait for them to get up to any top of any waiting list. We have our donor. And so we can just bring the donor in the operating room. And now we can go through with the transplant.

If they don't have a living donor, now we have to apply for UNOS MELD exception and we have to give them their chemotherapy. So here's the schedule and here's the maintenance chemotherapy. And that chemotherapy of capecitabine, by the way, is based on studies looking at palliative chemotherapy, chemotherapy for people with cholangiocarcinoma that cannot be treated in any other way. And the best results came from long term management with capecitabine. And that's why it's used as a maintenance chemotherapy.

But here's the schedule for somebody getting a MEL exception to be able to get a transplant. We get to put them-- this is after their exploration. We get to put them on the list at a MELD of 22. And three months later they can go to 25, and three months after that it's 28. Now in this part of the country for a blood type O, you need to have a MELD score above 35 or so.

For A it's about 30. So we're looking at a year of someone with cholangiocarcinoma and having chemotherapy to get to that point. And so here's the dropout. At six months, 30% of the people have fallen out. At one year. 50%. And that's what Mayo had shown early on. Most of these patients, if they have to wait a long time are not going to get to the point where they can be transplanted with somebody off the waiting list. Because it's just too grueling of a protocol to go through.

At the transplant, the last thing that we have to do is confirm a negative duct margin, because remember these tumors can grow along the duct down toward the pancreas? And we haven't assessed that yet. And then we can proceed with the transplant and decide what we need to do with the duct at the time.

So whenever we do one of these transplants, the first thing that we do is remove a segment of the bile duct down close toward the pancreas, give it to the pathologists and let them tell us OK, the tumor has not extended down to here. The first one of these that we did with a living donor transplant, the duct was positive. The nodes were negative. Person had gone through.

We have our donor in the next room. We can't get a positive margin. You go down a little bit further. Now we're into the pancreas, still positive margin. So in that case, we just proceeded with a Whipple. We'll take out the whole bile duct. And so this is from that operation.

This is a [INAUDIBLE]. That's the [INAUDIBLE] down here. The reason that you can see the whole portal [INAUDIBLE] back to the bifurcation that's [INAUDIBLE] is because the head of the pancreas is gone and the duodenum is gone. And the bile duct is. Gone and then we do the transplant. And then we reconstruct it all.

But that's-- you know, that's an option. It's an option that we have. And one that we can do when we have a living donor able to do it. Because this person is doing very well. Very high chance that we have cured this person by getting their duct out. But it means being at a center that's willing to get you through all of this and have a surgical team able to do this kind of an operation.

Afterward, post-transplant followup, we'll follow up with scans at three, six, nine, 12 months, 18 months, 24 months, and yearly up until five years. So they get scanned-- it's kind of the same protocol that we follow for patients with HCC. They'll get CA 19 9s. And of course they'll follow up with medical oncology and our transplant team.

So bottom line is cholangiocarcinoma is a lethal disease. It's a bad one. It takes a lot from the team and the patient to be able to get through the whole protocol. But live donor liver transplant is particularly important in these kind of patients. And that's all I have. So I'll take any questions that you have

[APPLAUSE]