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We're going to talk today about something very, very important for us as a program, which is HCC. And anyone who does this for a living knows that HCC is in every part of a liver transplant. And I'm going to take you through a little bit of the history of it and what we need to look at and what's in the future.

So number one, no matter what side of transplant you're on-- whether it's the medicine side, the surgical side, the oncology side-- HCC is on the rise. We're seeing more and more of it. We figured out, especially at this institution, that treatment options are centered around the tumor and have to be multidisciplinary.

And I will say that when you talk about how to treat HCC, it depends on where you're at. So what we do here is not what's done at a random podunk hospital in the middle of Arkansas, which is now what's done at UCSF. And it's dependent on what expertise you have and what options you have.

So whenever you hear someone say, this is exactly how I treat HCC, that's how they treat it at their place. So for example, there are centers that are excellent live donor, like we are. There are centers that do Mels of 22. And there are centers that have excellent taste guys. There are centers that do excellent resection.

So depending on what you have is actually how you treat these. So that being said, this is the only slide that I want you guys to take away. And then you guys can all go to sleep.

When you talk about HCC, the successful outcome is based on multidisciplinary action. So you've got to have a tumor board. You have to have all of us on the transplant side, because your surg-onc guy does not know what organ allocation is. He doesn't know what the new changes are going to be. He doesn't know what MELD they're transplanting at.

You have to know what your regional variation is. Your hepatologist has to be very involved with the cirrhosis, timely referral, listing, optimizing medical conditions. And you have to be able to look at the total tumor picture.

We have a lot of modalities on figuring out what your biology activity is. Everyone wants a very simple answer to a very complex question. It's not that simple.

So you have to look at the entire picture-- if this patient is cirrhotic, if they're actively drinking, do they have live donors? Are they going to follow up? Are they obese? Are they old? And then actually come together with a plan for successful treatment.

So in the US we are seeing a lot of cases. So we're seeing 1.5 to 6.2 cases per 100,000, which is actually a lot. That's actually increased. Back in the 1990s it was roughly about 9,000 patients. Currently we're seeing in the 2000s roughly 50,000 patients.

The median survival-- keep in mind we're seeing a nice filtered subset of patients. Right? We're seeing the people that are alive, following up, and can survive a treatment option. A majority of folks don't make it that far. And we never see them in transplant. Right? So the median survival is anywhere from two to eight months, depending on the 1, 5, and 10-year survival, even low as 0.8%.

We are getting better at treating them earlier as the decades go on. And we're getting better at treating them more with local regional therapy, which we'll talk about.

So HCC is endemic. We're seeing it more in the US. Even with our new antivirals, we have a huge rise in acute hep c. So we're going to be seeing this more and more even as we treat it.

And the first question that comes up is, how do I diagnosis this? How do you diagnose HCC? How do you figure it out? Is it ultrasound? Is it not?

And again, this comes back to the simple question of your center and where you live regionally predicts how you'll diagnosis this. So for example, if you're in Japan, where everyone has a BMI of 14, ultrasound works great. You can actually see everything pretty well. And the sensitivity is actually excellent.

Ultrasound actually has a sensitivity of roughly 58% to 89%, specificity of greater than 90%. Very operator-dependent. So if you're doing 1,000 ultrasounds a month, you get pretty good at finding HCC. If you're doing 10 ultrasounds a month, you get pretty bad at it.

CT works out pretty well. MRI works out also pretty well. And again, you have to keep in mind in Western Pennsylvania, not the land of the skinniest. We do have a Western PA body habitus, which is much better suited for CT and MRI than ultrasound.

Also, we have no data for surveillance. So we do have a lot of recommendations given out by ASLD. Currently the recommendations are-- which I do agree with-- are a single dynamic imaging modality. So either CT scan with contrast or MRI.

You're looking for intense arterial uptake and washout. Contrast ultrasounds aren't quite there yet. You can get some false positives, especially in cholangio patients. And even in our specialty center we actually see this in tumor board every week. Someone wants to biopsy a LI-RADS V. I will be pretty adamant about this. You don't need to biopsy a LI-RADS V. It's HCC. OK?

So even for UNOS guidelines, you do not need to biopsy anything. And the reason is, although biopsy has a specificity of 100%, it does not have a sensitivity of 100%. So if you miss it, it can still be HCC.

The tumor size matters. The needle size matters. There is always this option of tumor seeding, which means if you have a large tumor and you biopsy it that you seed the needle track on the way out.

So in the United States you do not need to have any type of tumor biopsy to get exception points and to treat. Other cancers are different. So for example, if you're treating a cholangio carcinoma, no oncologist will treat that unless you have a biopsy. If you have a colorectal mets adenocarcinoma of the liver, again, no one's going to give them systemic therapy without a biopsy.

HCC is very, very different. If you do have all the criteria and there are LI-RADS V, then you do not need any biopsy at all. You definitely have HCC.

Questions so far? Andres, anything?

No.

Good. OK, good.

So there are lots of cancer classifications. And again, HCC is unique. Unlike all cancers, which has-- we talk in a cancer classification system. So for example, breasts and colon and adrenal cancers all have staging and classification systems. HCC is uniquely different because you have cirrhosis. Right?

So you don't get HCC if you don't have cirrhosis. You might get a fiber lamella, but you only have HCC and cirrhosis. And both of those go hand-in-hand. So yes, it's two staging systems-- your cirrhosis and your outcomes with that, as well as your tumor size.

So again, there are a lot of classification systems. And any time you have this many classification systems, that means none of them really work.

So you have your CTP. You have your TNM, which is actually nonsense. You have a CLIP, you have a Chinese one, a Japanese one, Barcelona one. We don't have a UPitt one yet. But we're working on it.

The problem with all of these is they don't take into account both things. Right? So they don't take into account cirrhosis and what the options are.

So you have your TNM staging, which is basically based on your tumor size, metastatic disease, and your nodal status. That's great. But if you're a Childs C, it's a much different outcome than if you're a Childs A minus.

The best one to date is the Barcelona clinic liver classification system. It looks at the pathology, the liver function, the physical status, cancer-related symptoms. It's been done in Europe. It's also been replicated in the Western world. It's reproducible and very effectively predicts survival.

So briefly, you have a stage O, which again, is a Childs A with a very small tumor, a single tumor. You can go through several different options for that including resection, liver transplant, percutaneous ethanol injection, RFA TACE.

Now again, the key thing here is if you have portal hypertension, your only salvation is transplant. Only those that do not have portal hypertension should go on for a possibility of resection.

If you have a stage A through C, which means you have early A or B, if you have a single nodule, or you have intermediate tumor staging or advanced staging, you should go on for, again, liver transplant, PEI, or TACE.

If you had advanced stage, which means portal invasion, or you have a bad functional status, sorafenib or a systemic therapy is really your only survival option.

So again, where you live is dependent on what you see. So for example, if you look at this single tumor less than 2 in a Child's A, which all of you are shaking your head and shrugging your shoulders, because we don't see those folks. We don't know what that really means. And if you look at it, this is actually what represents a majority of cases elsewhere. In the US this is less than 10%.

If you have a single tumor, you have minimal cirrhosis, you have no portal hypertension, yes, you can do a resection with an 80% to 90% five-year survival or a liver transplant. There are no randomized controlled trials-- we talked about this selection a couple days ago-- that address first-line RFA.

There's a single study out of China which looks at less than 2-centimeter lesions. Again, if you have fibrosis and cirrhosis, and you get HCC, the odds that you'll have that happen again as a de Novo second tumor are actually high.

All right. So stage A again, liver transplant or resection. Stage B, TACE extends your time to 19 months. Median survival is 16 months or 50% at two years. And then Stage C and D basically mean that you have actually microvascular invasion, or you have a very, very poor functional status, in which case systemic therapy or palliative care are by far the best options.

All right. So the question always comes up. Should I go on to liver transplant or should I resect? I'm going to put away my liver transplant hat for a second because I do think that everyone should get transplanted.

And there are a very small subset of patients that do benefit from liver resection. But keep in mind, if you develop HCC, which is a disease because you cannot DNA repair in your liver, you're probably going to have another de Novo tumor. So if you have no cirrhosis, you can offer a resection. And there are relatively OK five-year survivals.

If you have Childs A, B, or C, which means you have cirrhosis, you should definitely go on for transplantation. This is actually a patient of mine. This is actually no tumor, and then about four months later, a lot of tumor. And again, we don't know what the resection rate is.

So resection does have intrahepatic recurrence rate. And keep in mind, if you have cirrhosis, you have diffuse disease throughout your liver. The inability to repair DNA which caused your first HCC is going to allow that to recur sometime in the future throughout the rest of it.

Transplantation works out well because it's oncologically superior. You are getting out all the tumor-- all the tumor you can't see, all the tumor that's not there yet. You're treating the portal hypertension. And you're eliminating the cirrhosis.

The problem is, we don't have an unlimited supply of livers. If we did, we would never talk about anything else besides transplantation for this. And when you go to Southeast Asia and other countries where they have no cadaveric system, yes, there are folks that don't have a live donor that actually have to alternate between getting a resection or a liver transplant.

All right. So again, this is the start of liver transplant, was not for cirrhosis, was not for anything else besides HCC that couldn't be safely resected. And if you guys get a chance, this paper is actually available. Actually, you can go to PubMed and click on the actual paper. It's a fascinating read. It's actually Starzl's first series of liver transplantation for cancer.

This looks at 41 patients who were transplanted for liver transplant for primary liver malignancy. So back then the thought was, the bigger the tumor, the more invasive the tumor, the best option would be liver transplant. You get out all the vessels. You get out all the tumor. You'll get out everything, and you'll put a brand new liver in. And voila, you're going to be great.

So six-month 43% mortality. Not really acceptable SRTR outcomes. But-- and a 25% three-year survival. But an initial good look at what not to do and why we don't do all tumors for liver transplant now.

Early on, same problem. If you looked at patient survival, hepatomic patients did far worse than any other subset of patients because we were using liver transplant as a means for treating people that had an unresectable tumor. So Childs A, MELD of 10 with a 16-centimeter tumor or a tumor invasive into the veins got a liver transplant, of course, had poor outcomes.

We slowly started to figure this out over decades, meaning '90s to the late '90s to early 2000s we figured out that larger and larger tumors were not the best. And we started minimizing the tumors. We didn't really have any criteria yet.

And keep in mind, back then liver transplant was a lot different. There was no MELD system. We gave out livers based on wait time. So we had a lot of people that were on the list.

You got extra points if you were in ICU or had a longer wait time. So we had a lot of people that were very, very young, very, very healthy waiting for a liver transplant and getting one. People that were sick missed out on their chance.

2002 came and dropped a MELD scoring system on us, so we couldn't really put in subjective criteria anymore. And yes, there was a lot of gaming of the system before this, not so much after this.

So now you had three criteria that predicted your 3-month survival on a transplant wait list. And to be honest, this is the only thing that MELD really predicts.

MELD is used for everything now. If you want to figure out if you can survive a dental procedure, look at this. And we have all these calculators now that predict survival from general surgery and cirrhosis.

MELD is only designed to predict your three-month survival on a liver transplant wait list. If your MELD is more than 40, your three-month mortality is above 70%. If your MELD is less than 9, your three-month mortality is less than 2%.

So at this point in time we figured out that we don't have unlimited supply of organs. We are figuring out that more and more people can get listed for liver transplant. And we really noted that the first initial foray into HCC and liver transplant didn't turn out so well.

So the most important trial, which came out back in 1996-- and for any of the residents or fellows back there, this is the ultimate retrospective study published in any GM. And it's been around now for 20 years as kind of the foundation of HCC. So this was Mazzaferro's famous trial was a retrospective study of 54 patients. It was not prospective. It was a retrospective study.

And they put in some criteria. So they looked and found that if you had three nodules three centimeters or less, a single lesion five centimeters or less, your five-year survival was good and your recurrence rate was good. And this came out at in any GM back in 1996. Four-year survival is 74%. Four-year recurrence-free survival, 83%. And this has been the basis of liver transplant in HCC in the US since that time.

So the Milan criteria we talked about. The exception points that we actually give folks now is if you have a T2 lesion that's within Milan and greater than two centimeters-- and again, you don't need a biopsy. All you need is very specific ATC criterion on your contrast-enhanced imaging, which is contrast enhancement with late arterial imaging. Then you can get exception points. And we'll talk about those in a second.

So the current stage two tumors actually get a MELD score exception of 28 after two months. And we'll talk about that in a second. If you are stage 3 or 4, what happens?

So you got a 15-centimeter tumor. Can you get listed for liver transplant? Deafening silence. Maybe? Hm?

Yes, you can. All right. But do you get exception? Absolutely not.

So you can do whatever you want. It's your program. So you can list every 20-centimeter tumor you want. You're not going go have very good outcomes, and you may not be doing a liver transplant much longer. But you can absolutely list whoever you like. But you only get exception for the people that fall within those criteria.

So if you're outside of Milan, yes, you can be listed. You just don't get exception points.

There are UCSF criteria. These are new criteria that came out after this period of time because a lot of people found that the tumor burden imposed by Milan was very conservative. People had great outcomes, but probably could be expanded upon.

So UCSF criteria is pretty simple. It looks at one lesion less than 6.5 centimeters, 2 to 3 lesions, none greater than 4.5, and a total diameter of less than 8 centimeters. And so what is all this trying to point out? All these tumor criteria, which by the way, even I have to look up UCSF criteria. No one knows this stuff and memorizes it the entire time.

What are these trying to figure out? Tumor biology, right? So you're trying to find a metric for tumor biology.

How bad is this tumor? Is it going to recur? Is it going to be bad? Is it going to be-- and tumor biology is not always a correlate of tumor size. So yes, we have 2-centimeter tumors, which I'll show you an example of in just a second that act like 15-centimeter tumors. And we have 10-centimeter tumors that act like 2-centimeter tumors. So it's not always a correlate exactly of size.

So UCSF looked at dropout. And again, there's regional wait time variance with this. So the six-month dropout was 7.2%. 12-month dropout of 37%, and 18-month dropout of 55%.

So keep that in mind. When you're looking at UCSF criteria, half of those patients grew to tumor outside of transplantable within 18 months. And California's nice for us in the academic world because they have a 24-month wait time. And they're also looking at transplanting only males above 35.

Other issues. What kind of liver did you get? Did you get a DCD? Did you have live donor options and get pulled off of this time?

And did we have a talk about allocation this time? I'll take that as a maybe. The deafening silence.

So just a quick highlight as we get hit with the concentric circles. Hopefully May 14. But we'll see.

So liver transplant is not fair. So where you live right now, your average MELD at transplant is 29.2. After May 14 that's supposed to go to 29.9 based on some modeling from really old data.

But if you live in Kansas, your MELD is going to be 22 at transplant. If you live in Indiana, 22. If you live in California, high 30s. If you live in New York, you're going to be happy to get a DCD at high 30s.

So it's very, very different, depends on where you live. And it's a combination of population density, how many centers are in that region, and what kind of donor availability you have.

Your chance of dying or getting a transplant depending on your MELD-- and we'll just focus on a MELD of 38. OK? Your chance of getting a MELD at a MELD of 38 ranges anywhere between 18% to 86% depending on what part of the country you live in. Your chance of dying goes 14% to 82% depending on where you live. OK.

So this throws out the entire MELD system, right? So your MELD is actually reflective of where you live. So a MELD of 38 is a lot different than a MELD of 38 somewhere else when you're looking at transplant.

So currently here's our problem. We have a lot of people on the list. They are sick. And they're going to have to get sicker before they get their transplant. We delist a lot of them because they get too sick. Their tumors grow outside of what we can transplant.

We transplant these guys. And anyone who's been on the transplant service for half a day knows they are sick, they don't get out of bed. We have a whole frailty section. It's a very, very long rehab road for these guys, no matter what kind of prehab we do. And we do need to have some reform.

So I'm going to bring up this patient here. This is actually an actual patient. NASH Cirrhosis. I did him about three years ago. So the MRI was a 3 by 1.7 LI-RADS V and a second 1.3-centimeter lesion. So within Milan.

We did RFA as a bridge to transplant. Native MELD was 18. Pretty healthy guy. And he actually had a very normal AFP and exceptioned up to a MELD of 28 and got a excellent liver transplant.

So briefly I'll have a couple of slides on bridge therapy just because we talk about this all the time. So there are different modalities of monitoring how your tumor biology is different on the wait list. So when you have a tumor of, say, 3 centimeters, like this guy, we really have no way to figure out is his tumor biology getting better or worse. And it's not a linear curve.

So we do things like measure tumor size, see if it's grown. And those are obvious things, right? So if your tumor goes from 3 centimeters to 8 centimeters in three months, doesn't take a rocket scientist to figure out you're probably going to do poorly.

But we do bridge therapy, which means local regional therapy, either TACE or RFA. We're mostly a TACE center here. We do occasional RFAs. Mostly it benefits people that have a wait time of more than six months. And there again, there is very good regional variation.

I'm going to fly through these UCF downsizing protocols. So UCSF did actually do a very nice study looking at downstaging. So they actually took people that within UCSF, downstaged them into within Milan.

They did this in a very nice perspective multi-center modality. They again had 34% dropout. 65% actually responded. 64% went on to liver transplant. And those who were downstaged and withheld their downstaging did actually very, very well.

The things that were predictive of having a really, really bad outcome were AFP. OK. So if your AFP is high, meaning above 1,000, above 100, above 400, you do very, very poorly on your downstaging. No matter what kind of downstaging you have, you actually have a very, very poor outcome.

So other things that we looked at-- risk of tumor recurrence for HCC. Usually that recurrence is actually happens in less than 24 months. We do follow up with routine imaging anywhere in AFP every 36 months.

There's a lot of shim shammery that happens. You know, maybe an mTOR inhibitor, or maybe I can put him on sorafenib which we use without a lot of evidence. Those actually have been proven to really not aid in anything. So mTOR, there's actually a nice trial that came out. There's a slightly lower recurrence rate and slightly improved survival, but nothing statistically significant.

Sorafenib has really no role for post-liver transplant. What do you think the benefit of sorafenib is? So that's NEXAVAR. It's our only systemic therapy for this. Hope the sorafenib rep isn't in here yet.

What's the benefit of sorafenib, which is approved? You look-- hm? Yeah. So it's actually you have a survival benefit of 9 months to 11 months on sorafenib. And that's only in Childs A with tumors less than 5 centimeters.

So not a really effective course. That's all that we really have, really no role in the post-liver transplant. And there actually was a trial out of UCLA which we participated in about three or four years ago. It all stopped because the recurrence rate was actually not impressive.

So when we do get recurrence, it's usually not the best. So in the setting of no graft cirrhosis or fibrosis, your really only option is TACE RFA. We really never resected anyone. You can try sorafenib, really no role in that.

You do get de Novo HCC, which is a liver that gets fibrosis again. And again you can treat the new tumor and possibly look at doing a re-transplant.

So again, you need to have multidisciplinary treatment, even on the post side. There is not one single person that is the best at this. You've got to have all of your minds together to get the best outcome.

Before when we used to have the 22 system-- so it was very nice. You got an initial score of 22. You got one extension, 25, 28, 29, 31, 33. And then you went to cap of 34. And the cap of 34 is important as the fellows know. At 34 I can't draw in from the region. So I can't pull livers out of Maryland or Philadelphia or anywhere else. It caps at 34.

Now we currently have a six-month extension at 28, which means you get a MELD of six for the first six months. And this is to prevent early listing with HCC to prevent dropout. So that allows the tumor time to say, you know what? I grew from 3 centimeters to 10 centimeters. Probably not a good idea to transplant me. And then I will never get to a MELD of 28.

Now at 28 we do get some offers occasionally, depending on which blood type. Not O. And then you go to 29, 31, 33, and again, a cap of 34.

So we're going to be doing a lot of changes in the UNOS world here shortly. Hopefully. So this is actually some proposed UNOS changes. We've actually had a big jump up in the number of HCCs that we've been doing.

There was a move to actually have HCC criteria auto-approved for single small lesions. So if you, again, met these single lesion between 2 and 3 centimeters, you had to get treated with local regional therapy. If it was completed treated, then you actually got automatically approved to get your exception criteria.

This was proposed about a year and a half ago. Completely denied 17 to 0. So that was shut down pretty nicely.

Next up was another auto approvals to actually have downstaging. This allowed people that had a single lesion less than five to eight, two or three less than five, or four to five less than three. They actually go through local regional therapy and downstage to T2 automatically get a MELD exception. This one, strangely enough, was approved unanimously. So this is actually in place now.

And then AFP has been coming up over and over again. And if you've looked at the literature recently, AFP is becoming a pretty good marker that we can use to predict your long-term outcome, especially those people that are downstaged. But if you look at a majority of transplants have an AFP of less than 200. And again, this is self-selection. If your AFP went up, usually grew you tumor out and automatically got removed from the list.

If you look at hazard ratios and mortality following liver transplant, it jumps up impressively at 200, but more impressively at 1,000. Then you can nicely predict your operative mortality in the first year after transplant based on your AFP.

So there was a proposal to actually make AFP greater than 1,000 ineligible for standard [INAUDIBLE] criteria exception. So if you hit 1,000 at any point in time during your process, you automatically no matter where your tumor is at that point in time could not receive actually HCC exception points. So this was approved and is in place now.

Biomarkers that are currently in place-- the G3 and EpCAM are actually showing some promise, but are not out there yet. AFP, we're seeing more and more numbers come out. If you pick your AFP number of 200, yes, you're going to probably be able to predict every recurrence. But you're not going to transmit a lot of folks.

If you pick your AFP of 1,000, yes, you're probably going to catch some recurrences. But you're going to let a few through as well.

The absolute contraindications, the things that we know for sure-- macrovascular invasion. This has been shown over and over again in any resection. If you have invasion in the great vessels or you have a larger tumor size, you're going to actually have recurrence. And you're going to do poorly no matter what treatment you get.

Back to our patient. So the liver explant shows things that are a lot different. Remember, he was within Milan on pre-transplant imaging. We were very happy with this.

So when we did the explant-- and HCC is different in liver transplant because every single patient gets a full explant pathology specimen. So we take the liver, we slice it, we look at every tumor that was and wasn't there, that every imaging picked and did not pick up. And we can actually also see how bad those tumors are.

So on his explant he actually had a 5.5-centimeter-- so outside of Milan-- a 1.1, 1.1 with some RFA necrosis. I was pretty happy because his surgical margins were free. That doesn't mean much.

About eight months later, pulmonary mets, and died about eight months after that. OK. And again, this is standard issue. This is what we deal with because we felt pretty good going in, met all of our criteria. We just don't understand the full ramifications of the disease. And we are not 100% on predicting tumor biology.

This is an interesting study that just came out. It's the Retreat study. And this actually uses AFP, vascular invasion from pathology, and the actual number of tumors. And so this is something that you can use to actually predict pretty reliably what your tumor recurrence is going to be not based on preoperative imaging, but based on the actual explant.

So again, pretty simple things. You got points for AFP, vascular invasion of viable tumors. And based on that score you're able to predict what your 3-month post-liver transplant survival is going to be-- anywhere from 58% to 91% based on exactly the number of tumors you have, how bad your lesions are, and if you have a vascular invasion.

So the future-- man. Identify these people for liver transplant early. I used to do HB in Cincinnati a lot. And over the past many years now sending people to liver transplant early is by far the best thing.

They get HCC for a reason because they have cirrhosis. Getting them to liver transplant, having a multidisciplinary team. If you ever wake up and you find yourself in a place that has one guy making the decision about HCC, you should leave that place. It's not the right way to do it.

We have a lot of egos, but no one is an expert at everything. It requires a lot of people to put their heads together. Even-- you know, even the social worker, even nutrition, behavioral, your medical oncologist. I usually mock our medical oncologists all the time, but they play a very important role in all of this because they can tell you what is really feasible. And they can laugh and say, Tevar, you're ridiculous. That's not feasible.

So that tumor board conference is very, very important. I think everyone should attend and be participants.

Markers of tumor biology. We're not there yet. We're using these surrogates like growth on the list, AFP, the things that have been around for 25 years. We are unable to predict exactly how our tumor is going to grow and what the tumor biology is.

And live donor liver transplant is a tool that we have here. It changes how we treat it. Because if you don't have live donor liver for that person, your treatment modalities are different than if you do. All right. Questions.