This is some of you may know only really recently joined the faculty at Yale. He is professor of radiology in biomedical imaging, and vice chair for clinical research at in the Department of radiology in biomedical imaging at the school of Madison. He received his doctorate at University of Pittsburg and did his residency trading at training at Suni Stony Brook and then additional fellowship in Vascular and Interventional radiology at.

University of Texas MD Anderson and David is really an international leader in advancing the work of of Interventional radiology in impacting both clinical care in clinical research in complex oncology problems and were really very fortunate to have recruited him to Department of radiology in the Cancer Center and he's going to share some of his on going work, particularly within the liver so David thank you.

These are my disclosures are none of which are actually relevant to this talk so I had gotten interested in liver regeneration back when I was at MD. Anderson this was like in the year 2000 when I had to present the complication of the procedure. But as you can see from these 2 cases. One would buy low bar colorectal metastasis and another with a huge HCC with multiple satellite nodules. We can actually take patients using liver generation strategies to get these patients, even just surgery or even treat.

These are my disclosures are none of which are actually relevant to this talk so I had gotten interested in liver regeneration back when I was at MD. Anderson this was like in the year 2000 when I had to present the complication of the procedure. But as you can see from these 2 cases. One would buy low bar colorectal metastasis and another with a huge HCC with multiple satellite nodules. We can actually take patients using liver generation strategies to get these patients, even just surgery or even treat.

These are my disclosures are none of which are actually relevant to this talk so I had gotten interested in liver regeneration back when I was at MD. Anderson this was like in the year 2000 when I had to present the complication of the procedure. But as you can see from these 2 cases. One would buy low bar colorectal metastasis and another with a huge HCC with multiple satellite nodules. We can actually take patients using liver generation strategies to get these patients, even just surgery or even treat.

Actually secure them and what I want to discuss today was methods for improving safety or even obviate the need for major liver resection. Unfortunately, due to the time constraints. I do have some work. I would like to show at some point and I cellular therapy for treating cirrhosis. We do have an animal model for sarot. Sis that we do want to place a tumor in and ultimately do some kinds of therapies for this. But at this time I don't really think it's possible so as you're all aware there have been tremendous advances. Incompatibility surgical techniques, such that death is now considered rare.
However, complications such as fluid retention, Costes is an imperative on theic function still contribute to prolong recovery times. An extended hospital stays. This is also true in the setting of Cirrhosis, where you can see patients that just have their right liver removed patients can have up to a 60% mortality, so in patients that have an HTC that need major surgery. You can see that there’s a need to help these patients get their surgery. Otherwise, they obviously would die without it.

One of the issues with having patients undergo surgery is the size of the remnant liver as you can see from this study from Paris is that there is a direct correlation between the size of the remnant liver and those that have complications now. This is not to say the overall type of complication, but it’s to show that the smaller the liver. The higher likelihood. You are of having complications that if you do know in advance that you may have a complication.

Chances are these patients will not undergo their surgery. Unfortunately, at this time, there’s still no limit to how small living room and you can have now previous studies have suggested that in order to reduce the morbidity hepatic resection about 20% of the liver mush remain in patients that have what you call normal underlying liver this for example, patients that have colorectal liver metastases never had chemotherapy writer. A section 20% injured liver. You need about 30% then we mean by that is patients that have had.

A lot of chemotherapy have Seattle hepatitis etc. And 40% of those patients that do have cirrhosis that’s actually where the normal underlying liver function. If you have abnormal liver function you actually need about 60% or you may not get surgery at all.

So we’re going to talk about briefly today is what I call preoperative strategies using liver generation with alphabet soup OK, so portal vein embolization is PV radiation lobectomy will get into is RL associating little partition portal vein ligation, which is a surgical procedure is called Alps and then we’re going to discuss later liver. Venus deprivation, which we will be having a clinical trial here starting in the near future, so in terms of historical perspectives.
Titan and what he did was he gave fire to the humans. Ultimately, helping them progress and Zeus, who I guess was the head of all the God Greek gods was very upset about this so he had a plan of giving him a punishment which was pecking at his liver every every evening and ultimately the liver grew back and this just got repeated and repeated and repeated which sounds like a very awful existence. However, we really didn’t know.

NOTE Confidence: 0.868499755859375

00:05:27.260 --> 00:05:58.670 That delivery generated experimentally until 1920 and this was a study from ruin. Larrymore, who found that portal being ligation and rabbits. If you ligate? What’s called the ipsilateral side. That means decide that you actually lie gated you get atrophy of that side and then you get hypertrophy or enlargement of the contralateral side. That’s decide that you did not like gate and this was also found to be shown in bile duct occlusion.

NOTE Confidence: 0.872407376766205

00:05:58.670 --> 00:06:30.180 Where that was shown in 19 in the 1950s in 1986 kamoshida published on doing PV before HTC reception. The fact is is that embolization of arterial embolization is not very effective against portal vein tumor thrombus so they thought that they could embolize the portal vein side that they could try to stop the growth of the portal vein tumor thrombus and as we know it’s portal in tumor thrombus that actually results in what patients prognosis is.

NOTE Confidence: 0.884233832359314

00:06:30.180 --> 00:07:02.820 In terms of liver cancer and then it was the Seminole work from Acouchi at the University of Tokyo. First performed portal vein embolization solely to initiate contralateral contralateral hypertrophy and 13. Patients with klatskin tumor when he found or the group found is that PV is saved as not complicate the surgical resection and liver failure is actually less common. After this procedure now in terms of Physiology, the activity hypertrophy complex is actually still to this day poorly understood. We know that there are essential components.

NOTE Confidence: 0.876994073390961

00:07:02.870 --> 00:07:33.040 We know that there’s a ability to be differentiating cleanly expand the liver cells not just the cell mass but also the cell number and that there’s multiple stimuli typography deliver. We also know that hepatocyte growth. Factor is the strongest mitogenic factor and is released from the parasites really in soon after had a sailor injury and gene induction can actually occur within the first 30 minutes an can last for quite awhile.

NOTE Confidence: 0.899135589599609

00:07:33.040 --> 00:08:02.820 But it’s the peak of Liberal Generation is within 7 days and then typically it returns to baseline now within 2 weeks and we also
know that patients that are diabetic because insulin is a cofactor with the parasite growth factor that those patients that have diabetes have less regenerative capacity. We also know that because patients with HCC have cirrhosis have very scarred livers and less flow through the liver they actually have reduced regenerative capacity.

NOTE Confidence: 0.865076005458832

00:08:03.470 --> 00:08:33.920 So, just to for this purpose of this talk. I want to go over some important terminology future liver. Remnant is what we’re going to talk about a lot and that’s anticipated liver parenchyma remaining inside too. After a section. We already talked about how much you need the degree of hypertrophy is a dynamic measure of liver regeneration such that if we look at the post FLR and we subtract the pre FL. Are we actually have what’s called the degree of hypertrophy and that let’s us know how well the liver generated and then kinetic growth rate is actually the degree of hypertrophy.

NOTE Confidence: 0.887810945510864

00:08:33.920 --> 00:08:51.450 Per week and we know based on some numbers or some data that there’s certain amounts of do we give hypertrophy an kinetic growth rate that will either allow patients to have surgery or we will say maybe this patient shouldn’t have surgery because their liver is not regenerating sufficiently.

NOTE Confidence: 0.881045818328857

00:08:52.010 --> 00:09:23.220 So what is portal vein embolization? Well, this is a strategy to redirect portal blood flow to the future living remnant an we can do what we can do here is initiate hypertrophy of the non embolized segments and ultimately the goal is to reduce perioperative complications and increase potential surgical candidates who have what we call marginal anticipated future live around and volumes. The goal is not necessarily to get better outcomes than patients that did not require PV E. However, the goal is really to get the patient to surgery so they have similar outcomes.

NOTE Confidence: 0.88483452796936

00:09:23.220 --> 00:09:31.720 Anne until recently, the consensus was that PV is the standard of care for safe and effective generation of FLR hypertrophied preoperatively worldwide.

NOTE Confidence: 0.868840932846069

00:09:32.300 --> 00:10:03.770 So we know from some clinical studies that the low bar function does shift from the non embolized. From the embolized to the non embolized lobe. After PV and we see some nuclear medicine studies showing that we also know in patients that have for example, class consumers where they have bilateral or BI Lo Bar Biliary drains that those patients that have PV E the amount of bio. That’s produced actually increases in the hypertrophy liver and decreases in the attribute liver.
And we also know from studied in the Anderson that you have less alterations in liver function test after reception following PV in terms of impact. There’s been 37 publications that were included in the meta analysis over 1000 patients and what they found was that the morbidity rate for these procedures is very, very low is a 0% mortality, although I’m not sure how accurate that is, and that most patients about 85% actually do undergo their plan to protect me what happened there Unfortunately.

There are some patients that either progress during the waiting period or don’t get sufficient regeneration such that they actually don’t become surgical candidates just to go briefly over some techniques. There’s a whole host of techniques that have been described we’re just going to talk about a couple of briefly, but this just shows that there’s standalone. An combination therapies. The original technique. That was described by Micucci was what’s called the Trans Elio College operative being approach, where they just can you lated Elio colleague vein threaded a catheter under Flores basic fluoroscopy up into the?

Portal vein and then injected the material and ultimately got portal vein embolization in the 90s. The first cutaneous approach was called the transit padded contralateral where you go directly into the liver from outside Percutaneously and as you can see one of the problems is that at the bottom here is that if you do get an injury to the liver remnants because you are going in through the liver remnant. This patient will no longer be a surgical candidate because if you have to embolize or treat deliver that’s bleeding.

You kind of hosed patient OK, so over the course of the last 2 decades. We’ve been very big supporters of actually accessing the liver transit attic, Lee through the liver. That’s going to be taken out and so that avoids ethyl our injury and you can see here. This is pseudo aneurysm that ultimately is respected at the time of surgery and it’s no big no big deal. This is actually a very multidisciplinary approach patients are seen by medical Oncologist Hepatologist Surgeons.

And in intervention radiologist, Interventional radiologists. This is not a very I wouldn’t say it’s a very glamorous type of procedure. It’s not arterial embolization. It’s not ablation where you’re the doing the definitive therapy. But you’re really working as part of a multidisciplinary team. We need to look at the patients underlying liver disease whether they have reduced regenerative capacity and if you’re unclear. You can do a
biopsy of the non tumors liver. We look at patients eyes with the understanding that larger patients require large liver elements such that liver standardization is critical.

NOTE Confidence: 0.887130200862885

00:12:38.650 --> 00:13:08.900 We look at the extent of panic and associated non appendix surgery as well as what we talked about earlier or some of the other factors such as whether patients with diabetes or pre emptive chemotherapy. This is just how we measure the liver. We only care about really the size of the liver remaining and I'll get to why that's important because if we look at this linear regression equation if you take the part of the liver that atrophy in the part of the liver that hypertrophy's you may get a denominator that changes. Overtime and ultimately you can get what looks like hypertrophy and actually you got none and the patient.

NOTE Confidence: 0.89014208316803

00:13:08.900 --> 00:13:41.010 After their PV if they didn't grow they have actually been found to die after procedures after the major surgery. So we used this very standardized formula where you see here you can see that the left lateral liver got much bigger after 4 weeks FLR increase in 1730% degree of hypertrophy was 13% and the kinetic growth rate, which is again divided by the weeks is 3.25% in terms of absolute contraindication is anything that would keep a patient from surgery is.

NOTE Confidence: 0.870726943016052

00:13:41.010 --> 00:14:11.300 Absolute such as over clinical portal hypertension. We also know that extensive portal vein invasions precludes safe. Catherine manipulation an embolic delivery as well as those that have complete low bar occlusion already have their portal being diverted and that’s how we know in a lot of cases that patients have cirrhosis for example, when they’re left liver grows huge in the old days. We used to have these some of these used to be considered absolute contraindication such as extra padding metastatic disease and tumor, invading the FLR.

NOTE Confidence: 0.863747954368591

00:14:11.300 --> 00:14:20.120 Or involving the FLR however, nowadays with much more aggressive surgery. We can see that these may not be there actually more now considered relative.

NOTE Confidence: 0.886324942111969

00:14:20.640 --> 00:14:44.080 There’s been only one study in the setting one prospective trial looking at the benefit of TV in the sitting at right headbutt. Ectomy in liver disease. You can see that based on all the parameters here, except death that this procedure does significantly improved postoperative course. This is one example 56 year old male, with HTC of hepatitis BNC.
We measured the FLR to be 33% which is too small as we said the patient had excellent growth so this patient was considered a candidate for right protected me. This is what the liver looks like Intraoperatively, where you see the left liver is huge and has very obtuse margins where the part that was embolized is very dusty and appearance and has very sharp, acute angles. So this patient ultimately had the surgery. Uneventful hospital course, however, did develop occurrence at 5 years and then underwent a successful transplant.

This was a study that we did during my days at MD Anderson, where we looked at patients with HTC and underlying liver disease and it’s only in those patients that did not have the PV. It did ultimately end up with dying from the surgery.

Now you can see here that 18% death rate not good.

And then if we look at HTC instead of chronic liver disease for survival. You can see that there’s very similar 5 year overall survivals and those that had versus those that didn’t importantly in those patients that had PV had. They not had PV they would have probably undergone chemo embolization or some other kind of procedure and only had a 20 to 30%. Three year overall survival. So you can see just by doing this procedure getting patient to surgery. You can actually improve their survival something that I discussed not too long ago but it seems to have gotten a lot of attention.

With something that we do call sequential arterial end portal embolization. This is actually separated by 3 to 4 weeks and the rationale here is that the capacity for liver generation after PV intersection may be impaired. So and that most HTC czar, hypervascular so if you do, do portal embolization. You’ll get Arty realization of the liver and the tumors will be inspired to grow and ultimately could take a patient out of respectability and then we also know that HCC and Cirrhosis has arterial portal shunts that could actually limit their generation after these types of procedure.

So this is just a case that I showed such that taste is followed by PV now should be considered as the standard of care for patients with chronic liver disease with HTC that before he protected me. This was just a study from Paris showing the benefit of PV and taste combined versus PB
alone. You get much better hypertrophy. You get an 83% complete pathologic response and the goal here is that you do really need to wait 3 weeks after the taste to reduce the risk of hepatic necrosis.

NOTE Confidence: 0.881507217884064

00:17:16.380 --> 00:17:51.390 It could occur by combining the arterial end portal. Ization’s and this was just a complementary study from Korea that showed very similar findings. They also found that you get significantly better overall and disease free of survival. This was one of the cases that I showed very early in the talk how we can basically take a patient that’s completely out of respectability an by doing arterial and portal embolization and then actually never even doing the surgery could lead to a very long survival. Now I’m not saying this would be done in every patient and the goal ultimately was to see if this patient could get surgery.

NOTE Confidence: 0.908893764019012

00:17:51.520 --> 00:17:57.910 But ultimately come in this case, we did not do surgery and maybe this is a way for definitive therapy.

NOTE Confidence: 0.887363851070404

00:17:58.700 --> 00:18:28.770 In terms of colorectal metastasis there’s also near equivalent to 5 year overall survival. As I had mentioned a little earlier. There is potential for or is concerned for this procedure, causing increase of tumor progression. And this just shows a prospective propensity score, matching where that was shown not to occur OK. This was a case that I also showed in the beginning, we would all say this patient is completely outside the realm of any kind of respectability.

NOTE Confidence: 0.852863132953644

00:18:28.770 --> 00:18:53.730 Multiple tumors throughout the entire liver as patient chemotherapy. The tumors got much smaller. We then did what’s called stage. One hepatectomy where they remove whatever would be tumor. That would be in the in the liver remnant. This patient had a 16% and as we said the patient really needs about 20% to get surgery. We did the PVE and the patient ultimately had successful surgery.

NOTE Confidence: 0.867942333221436

00:18:54.500 --> 00:19:15.080 This is a study that we did at MD. Anderson that shows Group One which is those patients that did not did not have tumor in their liver remnant and compared it to those that had need for a 2 stage protect domain and what we found was that 3 years that by doing this complex approach of two search protector mean we were able to get near equivalent 1 N, 3 or survivals.

NOTE Confidence: 0.91116601228714
And then this was a study that we published in JC. It showed in select patients that did make it to the second stage, we were able to get a 60% five year survival and again, these are very select patients. So I'm not saying that these are all comers. But those that didn't make it to the second stage.

There is a need for alternative approaches as I mentioned there are some patients that drop out or based on the lack of sufficient, Feller hypertrophy or tumor progression and one of the things that I'm sure you're interested in here is whether or not you can maintain patients on chemotherapy during the waiting period and the fact is that in the beginning of all this work. It was thought that the chemotherapy would, in fact damage deliver an impact the regeneration. However, it's now been shown.

That if you do chemotherapy after I mean before and during the waiting period after the portal vein embolization that there still is sufficient liver regeneration.

Some of the things that have been worked on is that if a patient does not do well after PV in terms of Regeneration. You can then embolize the padding vein. In addition to the portal vein OK that is actually causes what you would consider a bug, Kiarie approach and ultimately you get a very big liver ement if you embolize the portal vein followed by the patent beam.

And there's also been interested in happy to human poetic stem cells. So you would do the portal vein embolization. Then you would infuse themselves into the portal vein and it's been shown that you get much better hypertrophy. You get the addition of the stem cells that then turn into hepatocytes and you get much better outcomes. There's also been interested in what's called radiation lobectomy where you do? Why 90 radio embolization to deliver to invent to treat the tumors and it's been shown that over the course of time.

The deliver that was treated with the wine in the actually does get fibrotic and that causes the other side, the hypertrophy problem is that you don't really know based on the degree of hypertrophy and the kinetic growth rates. What if the patient can ever have their surgery. However, some of the components which includes Northwestern University.
Does think that this is like a test of time approach that you can see how the patients going to do if they get new tumors elsewhere and the other in the other lobe couple of last things there's been interest in a surgical technique to kind of completely take out Interventional radiology. This is a procedure that's done in 2 surgeries where they're trying to get massive hypertrophy very quickly so the patients don't fall out of surgical criteria.

What they do is they do the live around in surgery and then during that time they completely D vascular eyes segment 4, which is the medial left lobe of the liver and then they ligate the right portal vein and then you bring the patient back 7 to 10 days later and you ultimately have a massive hypertrophy, but the patient has very, very it's very, very morbid procedure.

So this is just looking at some data from MD. Anderson comparing it to the Alps procedure and you can see that the amount of hypertrophy and the time to get the hypertrophy is very, very rapid. However, they do have very, very high increased numbers of complications and even death.

What’s interesting here is that the liver may grow massively, however, if you look at electron microscopy for example, it turns out that the cells. Despite the fact that there are huge actually are immature and don't function like a normal liver cell.

So even though you get this massive hypertrophy and we're looking at the volumes the functional capacity of those areas may not be that great and this is just a meta analysis just showing that that helps the kinetic growth rate does grow. In fact faster. However, there is much more overall morbidity and mortality, so apps may be suitable. You really need to consider the Morbidity and mortality before doing these complex surgeries. Lastly, I talked about liver Venus deprivation.

This is based on the padding vein embolization and the portal vein embolization that we had just discussed the goal here was to shorten. The time between the two procedures to get patients 2 surgery. It has been shown that this is now a feasible approach an that if you look at this part here where you place. You do portal vein embolization and then you place plugs and other material into the hepatic the right of Haddock militating veins.
You can get almost to the point of hypertrophy that you would get with the Alps procedure. But it has been shown already that it may be that they function cells function better 'cause. It does take a little bit longer to do.

One thing I wanted to show is that there will be a clinical trial that we're doing here at you know, I'm going to be the with Charles Cha from surgery is the Co Pi. This is called Dragon one in Dragon, 2 dragon. One is where we're just doing a feasibility study and then Dragon, 2, is taking the liver venous deprivation and comparing it to portal vein embolization alone, so that's something that's going to be starting here, probably in January, so In conclusion.

I hope to have shown a very, very quickly that liberal generation is critical to manage in patients with primary and metastatic liver cancer and that there are numerous strategies that exist to regenerate liver. Villa Ricca Tenya's in surgical means. I do have some very exciting stuff that I think maybe some other venue. I can talk about which has to do with some cellular therapies and other methods in an animal model to do this. But for the purpose here. I think that I wanted to get you all interested in the fact that.

Interventional radiology does more than oblations biopsies. Other embolization's and that I think that there's a lot of opportunity for collaboration and growth so with that. I think I'll stop here. Thank you for your attention.

Thank you open it up so when when looking at these approaches like PV are there studies or efforts where you could introduce additionally pharmacologic interventions? Absolutely that could improve efficacy that currently has been introduced in infusing hepatocyte growth factor for example, directly into the liver there's been other.

Agents that have been used there's even been what's called I took out a lot of this stuff for the purpose of the time, but there's even been interested in what's called reversible. PV so one of one of the problems with PV is being that it's a very definitive therapy. So if the patient doesn't get respected can you still give a transarterial therapy so there's been interest in what's called reversible PV which has been published in the Journal of Hepatology and then.
Because most of their generation recurs within the 7 to 14 day window. You can even repeat that so there’s been interest in that. But in terms of formal echologics. The answer is absolutely that there is interest. But it’s also about some of the problems are that if you do it in animals. There are typically always in normal liver and they don’t have tumors in them, so you don’t really want to do this in the absence of a clinical trial and just getting patients into these clinical trials has been kind of difficult.

As I said there’s been only one clinical trial that showed the benefit of portal vein embolization compared to know portal vein embolization and the reason why that is, is that it’s an ethical dilemma. For a surgeon to do a procedure on a patient or do I surgery on a patient when they figured they could have had a PV E, but then because of the trial didn’t and then they died so you know, but the answer is yes.

Chemotherapy during the week. There’s that affect the functionality of the regenerated liver.

Regenerated cells are as their work on that front. I know it merely standings.

But it is the body of the well. That’s a little bit unclear. There is you know, some chemotherapies that damage the liver parenchyma more than others, like Sally Platten for example.

There’s also been studies that have shown that if you give more than or I should say if you give less than 3 months of chemotherapy. The patients actually do better after surgery than if they have cycles. They go beyond the three months, so that was a study that was published MD. Anderson my former group, so the answer to that is probably yes, but I don’t know if there’s there has to be. I’m sure a basis for that.

Today we thank you that that was really instructive.