[MUSIC PLAYING]

JOHN RENZ: I did this a little bit different than the earlier presentations. I basically got the DDW book, and then used the following key words to identify all abstracts under those keywords, read them, and then reorganized it by category to try to briefly go through the abstracts, and distill them into a little nugget that we can then tie to a unified theme. About 18% of the abstracts that were reviewed will be shown to you though.

Of course, we have to establish the ground work in that the first and foremost thing is that hepatocelular carcinoma is rising in incidence. It's the sixth most common GI cancer in the United States. And it's the cancer that has the highest incidence of mortality with respect to rising acceleration.

The reason is probably multifactorial, as to the rising incidence of HCC. It involves the classic normal itis-osis-oma paradigm. And likely it's the result of improved GI management of cirrhosis. The cirrhotics live longer, and they're healthier. And as a result they get more HCC.

Now there's a lot of therapies out there for hepatocelular carcinoma. And there is some regionality and an institution specificity. But we'll basically go through these in the abstracts. I just wanted to go through a couple of them so that we're all on the same playing field.

The only curative modalities are surgical resection and orthotopic liver transplantation. Chemotherapy is budding under sorafenib, and local regional therapy is varied in its deployment, but it's generally overall considered a bridge to either transplantation or to prolong survival, but not to change the outcome.

When you look at the treatment schedule, it's really dictated by what's called the Barcelona Clinic Liver scheme, and it's a really complicated slide. But it can be distilled down into whether or not the patient has decompensated cirrhosis, and is overall a candidate for either resection or transplantation. If that's not in the cards, then you're left with local regional therapy, which can be multivariable. And we'll go through this at the end, after we go through the abstracts, to try to distill it down into a very easy formula to manage the patient.

The last thing to know before we get into the abstracts is what is the Milan Criteria, and how does it affect liver transplantation? At the end of the day, we can transplant anyone we like for hepatocellular carcinoma. The Milan criteria simply allows that patient to be brought up the list without having to have a decline in physiology. There are some insurers which will restrict the Milan criteria. But the general thinking is that it's more important to understand the biology of the tumor than to be preoccupied with whether or not the tumor is within the Milan criteria.

When we talk about the Milan criteria, it is one tumor up to 5 centimeters in diameter. Or no more than three tumors each of which is less than or equal to 3 centimeters in diameter. And if your patient is within Milan criteria, the importance of that is that if they go to transplantation, their survival will be identical to those patients receiving a liver transplant we do not have liver cancer at all. So the overall outcome of those patients is identical. And therefore, those patients are prioritized on the liver transplant waiting list.

So with that, we'll get into some of the abstracts. We'll just quickly go through these. There was a lot in screening and demographics. And the first two abstracts were very interesting. They were done by the group in Parkland. And they looked at primary care providers, and what their surveillance patterns were, and what the outcome was of those patients who they ultimately identified had hepatocelluar carcinoma and how they did.

The first abstract looked at primary care physicians versus gastroenterologists, and asked the question, what was their surveillance strategy. And in this group only 52% of the primary care providers were using ultrasound and AFP as their surveillance tool. Over 45% used either physical exam, liver function tests, or only alpha fetoprotein. So this led the authors to conclude that the primary care physicians were really not up to date as to what the current criteria are for HCC screening.

They then took the same cohort of patients, and looked at those patients who had HCC, and retrospectively looked at what actually was done for those patients prior to the diagnosis. And only 15% of those patients who'd been managed by the primary care providers had had screening which met the current AASLD guidelines. About 55% had some kind of screening on an annual basis, and that some kind could be anything as simple as liver function test. And the remaining roughly quarter had no screening at all. So the first two abstracts really were helpful in showing just how big the problem was with respect to surveillance for HCC screening.

The next two, the first one was a SEER database, looking at people who had HCC, and what were some of the racial disparities, and also geographic disparities in their diagnosis. So they looked at the SEER database, which is a national database. And they group people according to African American, Caucasian, Asian, or Native American. And they looked at the initial timing of the diagnosis of HCC, and what their outcome was. And then they correlated that to the area of the country that they were located in.

And when you look at those four groups, unfortunately African Americans have by far a poorer survival than the other three groups, when they're diagnosed with HCC. And not surprisingly, they're diagnosed at a much later stage of HCC, and with more metastatic disease.

When you look at the tumor burden within the liver at the time a presentation, interestingly the Asian group had a higher tumor burden at presentation. But that did not impact their long-term survival.

The Sa1048, sorry I don't have a pointer. But that one looked at some of the racial difference, did the exact same study. It was a single-center study; however, looking at NAFLD, and look at the different racial groups and what their presentation was with NAFLD. And interestingly in that group, although it's a single center, they did about 300 patients in that study. It showed that when you looked at Hispanic patients, Hispanic patients generally presented with a higher degree of cirrhosis, a higher MELD, and a higher incidence of HCC, when they presented to their institution and were diagnosed with non-alcoholic fatty liver disease. When this kind of bolsters the emerging data that NAFLD in the non-Caucasian population may have a more malignant, if you will, phenotype, or a phenotype associated with more morbidity.

The next study I put in there is actually a Taiwanese study that looked at screening for HCC in Taiwan. And it was the perfect comparison to the Parkland study. And there they were looking at what their screening results were. And interestingly in their cohort, which was a Taiwanese national database, they had 65% of the patients diagnosed with HCC were diagnosed under AASLD guidelines. That's a pretty stark contrast to what's going on in the US.

And when they looked at those patients, and predictors for diagnosis, they found that patients who had a family history of HCC, not surprising, or more office visits to their primary care provider, had a higher incidence of diagnosis at a lower tumor burden.

When you think about HCC, one of the things we worry about is the idea of incidental HCC. And that was explored in the Mo1056 abstract. This was a single-center experience that looked at what is the outcome of incidental HCCs discovered at the time of liver transplantation. And that data has been quite variable over the last 10 years.

In this group, they found interestingly that the incidentals did not behave the same as patients who didn't have cancer at all. Which is a novel finding, and counter intuitive to what the dictum has been in the United States. But that the incidentals behaved more like patients with known tumors, whether they were within or outside of Milan. So that actually is different than what we've been practicing in the US, and deserves kind of further study.

For chemotherapy, of course that's dominated by sorafenib. So we'll quickly go through some of the things that sorafenib has been shown to affect with respect to patients with HCC. The first one, which is a very interesting study that I haven't seen looked at before and that was Mo1039, which shows patients we give sorafenib to almost always have some kind of complication. And that's not news. But is the type of complication they have linked to somehow responsiveness to therapy?

And they did a very nice study which looked at the different complications. The most common complications were diarrhea, fatigue, and hand-foot skin syndrome, and tried to correlate those complications with response to therapy. And in the end, it turns out that these patients who were on sorafenib, the occurrence of hand-foot in skin syndrome and hypertension positively correlated with response to therapy. And indeed in that group, they had about twice as long of survival as patients who had a complication but not either of those two.

And then amongst the small group, only about 20% of the patients who were in the study had no complication. Their outcome was the same as those patients who had a complication that was not hand-foot in skin syndrome, or hypertension. So it looks like patients who have one of those two may be predictors for improved survival.

When you look at-- this is Mo1055, what are some of the things that will predict response using resist criteria when we start our patients on sorafenib? And the bottom line is a dramatic reduction, the author said more than 50% reduction in alpha fetoprotein in the first month, or well-differentiated histology predicted tumor response, using resist criteria. So that's another way to get an early handle on our patients, as to whether or not it's likely they will respond to the sorafenib therapy.

When you look at the final one, Mo1058, it looked at patients-- this abstract was not as it appeared on the title. But I thought its take-home message was good. It talks about survival. They're going to see a survival difference. What they were trying to say is what are the predictors when we start a patient on sorafenib that they will ultimately complete the therapy, and not have to be dose eliminated.

Because throughout the DDW, the average rate of discontinuation of the drug was anywhere between about 35 and 45%. So what can we do? How can we predict those patients will get through with simply just dose reduction, rather than eliminating the drug? And the bottom line was it came down to ECOG performance status. Interestingly, alcoholic liver disease had a much higher incidence of getting through sorafenib therapy, or Child-Pugh score or MELD. So that's kind of intuitive. The healthier they are, the more likely we'll get them through.

In the world of transplantation there was some interesting things. We don't do a lot of transplantation in the room. So I'll just kind of categorized them very straightforward. The effect of preoperative transarterial chemoembolization, there is no effect of preoperative chemoembolization. And that's been shown over and over in the United States. And whenever you have a waiting time for a liver of more than six months, there might an effect of TACE, but if you're transplanting within six months of diagnosis, whether or not they receive local regional therapy has no impact on survival. And that's exactly what these authors showed.

Interestingly, in Sa1023, they looked at patients who received liver transplants both within and outside of Milan. And I put this in because the group within Milan, expectedly, got about 85% one-year survival, which is what you'd expect. The group outside of Milan, only had about a 45% incidence of one-year survival. And the major incidence of recurrence was HCC. I put that in, because that's not what we see today. Today actually we get much better survival in patients undergoing a liver transplant outside Milan criteria than we have historically. And that abstract is based on 15 years of data.

So I think the take-home message when you look at HCC and liver transplantation is that in many ways size doesn't matter. It's really about biology. And it's our duty to the patient to figure the biology out. And then offer the patients who we think have favorable biology a transplant.

477 is an interesting abstract to look at when you have a patient who's had a liver transplant and they have recurrence of HCC, should you give them local regional versus sorafenib. And overwhelming, the data shows it should be sorafenib. Recurrence of HCC in a transplanted liver is systemic disease. And it should be treated as such.

In fact, the patients who get local regional therapy generally have inferior outcomes than those patients who received no treatment alone. And the reason is because local regional therapy in the transplanted liver can be dicey, especially TACE. Because a lot of anastomoses the are there, and in the donor transplanted alograph there's a lot of atherosclerosis and vascular injury as the graph goes further and further from transplantation, secondary to the calcineurin inhibitors. So if you have a patient who had a transplant, and has HCC, they need to go directly to systemic therapy, and shouldn't receive any local regional at all.

Lastly, in the transplant, it's very exciting news in the transplant community. We're getting to the point where we can start giving liver transplantations to patients with cholangiocarcinoma. That was a taboo for the last decade. And this abstract very nicely showed the difference between patients who have enteropathic cholangiocarcinoma who get a liver transplant, versus resection, versus liver-directed therapy.

Now it's not an apples-to-apples comparison. But the interesting thing is that they were getting about 70% one-year survival in their transplant group, which is close to what we get for other liver transplant recipients. And in the resection group, they were only getting about 40% one-year survival. And when they were doing intent-to-cure surgery, they were only getting N zero resections at about 30% of the time.

Which is intuitive, we're not as good as we'd like to think surgically at treating cholangio. And it's probably better to move toward transplant. Those patients are getting neoadjuvant chemotherapy, and that's making the difference in again selecting biology that favors liver transplantation.

Liver surgery, I put this in just to kind of round out the disease categories I was given. This was a really nice study, Su1819. It looks at patients who undergo resection. Can we predict using the MELD score, what they're outcomes will be? And indeed, we've always had the Child-Pugh score. But the Child-Pugh isn't really that sensitive.

And indeed, when you look at MELD scores in patients undergoing resection for HCC, it looks like optimal outcomes are achieved to about a MELD of 18. And the higher the MELD off of 18, the more precipitous the outcome. So it was nice to see that the MELD was replacing the Child-Pugh score, at least within the general surgery literature, in order to dovetail that with outcomes. And single-digit MELD scores, all the way up actually to 11, did not affect the patient's outcome. They all did well after resection. And an 11 is almost always a Child's B. And the B was always kind of the gray zone in general surgery. So I think MELD is much more sensitive to determine a patient's candidacy for resection.

And then lastly sorafenib use after surgical resection or transplant in HCC, this is the Gideon study, which is an international study. And the take-home message is that has not been shown yet to make a difference. There are lots of isolated center reports that are showing difference. But international data still has not shown a difference in adjuvant therapy using sorafenib.

Three last markers, tumor biology, where we're going in the future. Microvascular invasion, we can't predict this pretransplant. It's a bad outcome posttransplant. And this was a Hopkins abstract that looked at some of the predictors. They looked at MELD. They like that AFP, inside or out Milan. And the most interesting, or most sensitive indicators to microvascular disease was bilobar tumor distribution within the Milan criteria. So that's something to keep in the back of our heads.

Su1472, it looked at the question when you have a patient who has an HCC rupture, should they receive surgery. And the answer is no. The outcomes were identical to those patients who had HCC rupture, were treated with TACE plus systemic therapy, versus those patients who had an HCC rupture and received surgical resection. And that's not counting the morbidity associated with surgery. So HCC, a ruptured HCC is T4 disease, and should be treated systemically.

Mo1041, this is the last thing. And there was a recurring theme, both in the DDW, in the recent ILTS meetings in London, and in the AASLD last year, the rise of AFP again, the meaning of AFP. I mean I think AFP is important. I know the studies don't really say that. But the reality is when you follow AFPs, and AFPs change, something's going on. And there was a beautiful study both here and at the ILTS, that showed that rising AFP in addition to imaging, increases the sensitivity of both CT and MR imaging. So I think the story for AFP is getting better, and not worse, and that I think it's still useful when you look at it serially.

So to go back and just try to make heads or tails out of all those abstracts, it really comes down to how do you choose your weapons. And this slide really summarizes it the easiest. If you have a decompensated cirrhotic, it's really only about transplant if you're talking about a cure. In a non cirrhotic, or a cirrhotic that's well-preserved, say MELD less than 15, there's a lot of options open.

And I think in that situation, ideology is important. If the patient's undergoing continuing liver injury from hemochromatosis, or an underlying metabolic disease, then transplantation is probably your best route. Where if the patient does not have continuing undergoing injury like ALD, and they're now abstinent, or they have hepatitis C and they've been treated, then surgical resection is probably your best way to go, even if it means a more difficult surgical resection.

And that is different, because the transplanters were quick to go to liver transplantation, I think, historically. But with the understanding that salvage transplantation, meaning transplant after resection, is a very poor outcome, especially in patients with ongoing liver injury. Those schemes are changing.

Small tumor should always be treated with resection, be it laparoscopic or open. And those patients without surgical candidates, really for local regional therapy I think it's really institution dependent. And I think practically speaking, all the therapies are the same. Locally advanced deals with ablative and metastatic disease, of course, is the realm of sorafenib.

So at last, we just kind of tie it all together. You see we have a very comprehensive liver cancer center. We do wonderful multidisciplinary care. We have all the most innovative therapies going on, whether it's laparoscopic liver resections. We're doing lot of neoadjuvant chemotherapy for patients with advanced HCC, and cholangio, and those patients are being considered for liver transportation once we understand the biology. So with that, thank you very much for your attention.