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Reducing the Risk of Hepatocellular Carcinoma in Hepatitis B & C

Announcer:
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Dr. Lim:
On behalf of the Asian Health Foundation, I'm pleased to welcome you to "MedTalk 3: Reducing the Risk of Hepatocellular Carcinoma in Patients with Hepatitis B and Hepatitis C Infection." I'm Joseph Lim, Professor of Medicine and Director of the Viral Hepatitis Program at The Yale School of Medicine. I'm pleased to introduce my faculty colleagues on the panel, Dr. David Bernstein, Professor and Vice Chair of Medicine and Chief of Hepatology at the Zucker School of Medicine at Hofstra/Northwell, and Dr. Andrew Muir, Professor of Medicine and Chief of Gastroenterology at The Duke University School of Medicine. Welcome, gentlemen.

Dr. Muir/Dr. Bernstein:
Thank you.

Dr. Lim:
Today, we are hoping to review a topic that is near and dear to our hearts, which is reducing the burden of liver cancer in patients with hepatitis B and C infections. We understand that the burden of liver cancer is substantial. It is the number 5 most common cancer globally and the number 3 cause of cancer-related mortality. And, we know very well that the incidence of liver cancer in the United States continues to grow. We know furthermore, that this is predominantly driven globally by hepatitis B and here in the United States by hepatitis C cirrhosis. What we hope to do today is talk through the current state of the art in the management of hepatitis B and C as it relates to reducing the risk of liver cancer.

First, we'll discuss the impact of antiviral therapy on liver outcomes, including liver cancer. Two, risk stratification for liver cancer in patients with hepatitis B and C: what are the major risk factors? And finally, three, the current approach to surveillance for liver cancer in patients with hepatitis B and C.

We're going to first talk about the impact of antiviral therapy. I want to start with hepatitis B, and I'll direct this to Dr. Bernstein. David, tell us what we know in 2020 about the impact of antivirals for hepatitis B and its impact on liver cancer risk.

Dr. Bernstein:
I think, Joe, in order to best review what antiviral therapy for hepatitis B has done, it's important to understand first that these are simple therapies to use and they have a tremendous impact in bringing down viral load. And since we know that there are certain risk factors for the development of hepatocellular carcinoma in hepatitis B, such as high viral load or cirrhosis, what's happened with these oral agents is they actually have been shown to bring the viral load down, which decreases the risk of hepatocellular carcinoma. In addition, they've shown an improvement in degree of fibrosis, with even patients who had cirrhosis becoming non-cirrhotic and therefore also

reducing the risk of hepatocellular carcinoma. So, these antiviral therapies for hepatitis B have been shown to decrease the risk of hepatocellular carcinoma in patients with hepatitis B.

Dr. Lim:
Thank you, Dr. Bernstein. Do we know any information about the ongoing risk of liver cancer in those who are virally suppressed? And, are there differences between antiviral agents in their ability to reduce cancer risk?

Dr. Bernstein:
We know that if we bring the viral load down and even make it undetectable, the risk of hepatocellular carcinoma does drop significantly, but it doesn't go away. ~~-~~Therefore, it's important to continue to screen. To date, there aren't any significant differences with the current available therapies for improvement in the risk of developing hepatocellular carcinoma. They're all the same.

Dr. Lim:
So regardless of the antiviral agent, regardless whether it's a nucleoside or nucleotide analog such as entecavir/tenofovir, there do not appear to be meaningful differences if the key is virologic suppression as the way that it's mediated to reduce cancer risk. So, thank you for that helpful response.

Dr. Bernstein:
Thank you.

Dr. Lim:
Dr. Muir, I'm going to ask you about the impact of directly acting antivirals for hepatitis C and their impact on liver outcomes, including liver cancer.

Dr. Muir:
Thanks Joe. I think this is really one of the important things for our patients to be aware of, that they can, through cure of their hepatitis C, reduce their risk of cancer. It was actually challenging to know this for quite a while because hepatitis C has such a long natural history and to really know that we're having an effect. And one of the landmark studies that was published back in *JAMA* in 2012, the first author is van der Meer, looked at five centers in Europe and Canada and at 530 patients and were able to go through their charts and follow them for about 8 years. And what they found is that there was a big reduction in liver cancer. To David's earlier point, it doesn't go away, but it's a significant reduction.

That study showed other benefits, including liver-related mortality and actually all-[cause] mortality but that liver cancer reduction was particularly meaningful. There's been some controversy over the last few years about risk of liver cancer with some of these agents but I think through some good work that's been done by a number of groups, including through the VA and some systematic reviews now, we have ~~a~~ strong confidence that liver cancer risk is reduced through cure of hepatitis C with the direct-acting antiviral agents that are available.

Dr. Lim:
Fantastic. Obviously, our ability to cure hepatitis C and reduce the risk of cirrhosis, decompensation, liver cancer and both liver and all-cause mortality has had a huge impact on the burden of hepatitis C in this country. I think the message is clear from both of you that antiviral therapy is actually quite beneficial in reducing but not eliminating the risk of liver cancer. Therefore, what we'll be discussing momentarily is who are the individuals who continue to be at risk, requiring ongoing surveillance. We're going to now transition to the second topic, which is risk stratification. The goal here is to outline for our listeners what are the major risk factors for liver cancer in a patient with hepatitis B and hepatitis C that should help inform where surveillance is most beneficial.

Dr. Lim:
So, let's get started with hepatitis B. David, what are some of the major risk factors for liver cancer in patients with HBV?

Dr. Bernstein:
I think it's important to understand first and foremost that anyone with hepatitis B is at risk. But, when you look at certain other risk factors, those patients that have a high viral load, considered more than 200,000 IU, those with more advanced fibrosis and cirrhosis are at greater risk. Patients who are e-antigen positive are at greater risk. Those with a family history of liver cancer are at a greater risk. And also, if you're going to genotype – and we really don't recommend genotyping hepatitis B – those with genotype C are at greater risk of developing primary liver cancer. I really think the important thing about hepatitis B is to remember unlike other conditions is that you can develop liver cancer in the absence of cirrhosis. And, you can develop liver cancer even with lower levels of virus. So, you have to really think about all patients with hepatitis B are potentially at risk for developing primary liver cancer and screen accordingly~~-~~

Dr. Lim:
Perfect. So, let's transition to hepatitis C. Andrew, you want to talk us through those risk factors?

Dr. Muir:
One of the differences between hepatitis B and hepatitis C is that with hepatitis C, you don't see that risk of developing liver cancer in the early stage patients. So, we're really focused here on patients who have advanced fibrosis or cirrhosis. And in that group, we can cure all these people, right? So, after we've cured them, who are we still monitoring? Who are we still really worried about for the development of liver cancer? And I think about things that could be going on in their liver, so do they have diabetes and possibly fatty liver disease? Are they drinking alcohol as another insult? Are they obese, again, for that insult for fatty liver? What could they be doing to improve their liver status, decrease the likelihood of developing liver cancer?

The other group to remember, though, is patients infected with HIV and hepatitis C. That group has a more aggressive natural history. That group has increased risk of liver cancer, so again both their HIV and their hepatitis C need to be well treated, and they need close monitoring as well.

Dr. Lim:
Excellent. That's very helpful and naturally lends itself to a discussion about who we screen for liver cancer, and how. And so what I'd like to do is again walk through, who are the patients that are currently recommended by our GI and liver societies for liver cancer screening and we'll talk through hepatitis B and C, and then I'd like to close with a conversation about, you and I are doing in terms of personal approach to how we test, what tests we use and how often. Let's turn to Dr. Bernstein. Who should we screen for liver cancer in a patient with HBV?

Dr. Bernstein:
So here I think it can become very confusing if one reads the various guidelines. T]he American Association for the Study of Liver Disease, the European Association for the Study of Liver Disease, and the Asia-Pacific societies all have guidelines for screening for hepatocellular carcinoma in patients with hepatitis B. And, they all have some similarities, but they also have some differences. I think the differences are sometimes difficult, meaning some recommend starting at age 40. Some recommend starting at age 50. Some differentiate between male and female. So, I think we have to go back to, from a simplicity standpoint, who's at highest risk? Those with high viral load, those that are cirrhotic, and those that have a strong family history of liver cancer. And remember that with hepatitis B, anyone can develop hepatocellular carcinoma.

So, I take the approach that we should be screening everyone who has hepatitis B, regardless of age, every six months with an imaging study, usually an abdominal sonogram, and an alpha-fetoprotein. That may be a little bit radical, but if you screen everybody, you're not going to forget and you're going to find tumors that you can treat – sometimes surgically, sometimes radiology, sometimes transplantation. But I would advocate screening everyone with hepatitis B every six months.

Dr. Lim:
Fantastic. This is very helpful because what I'd like to do is bring in our whole group to discuss what is it that we actually do in the real world. The AASLD does recommend age-based cut-offs for Asian men greater than age 40, Asian females greater than age 50, family history of liver cancer, as well as Africans at a younger age, potentially as young as age 20, and then all patients with cirrhosis. However, as you have described, and is certainly consistent with my own clinical practice, I tend to screen all patients, recognizing that there are individuals who will be missed based on those traditional cut-offs. So, I want to transition to Dr. Muir. I first want to ask you, what is your current approach to surveillance in hepatitis B, as well as your initial comments about the patients who should be screened with hepatitis C?

Dr. Muir:
So, my general approach with hepatitis B patients is really to talk to them. I generally follow what the guidelines say based upon the age cut-off that you already outlined. I think for the patients who don't fall into the age cut-off, I like to have a conversation with them about what the surveillance program would look like, what that would mean to them. For some patients, that's very reassuring; for other patients, it's not. And, so, I really like to make that part of a shared decision-making plan. I find that many patients prefer to go ahead with the surveillance, but I don't want them to feel forced into it if they don't fit into one of the groups that are outlined in the guidelines.

As far as hepatitis C, it's a very different strategy and I think one of the important things for that group is to say who I do not screen. So, I do not screen patients who have early stage hepatitis C and they are not at risk for developing liver cancer. That's just a clear finding and so that is also one of the reasons why it's so important that all patients with a diagnosis of hepatitis C get some kind of assessment for how much fibrosis they have, whether it's a blood test – we used to do liver biopsies; we don't do those very much anymore. One of the elastography tests, which is what we use a lot of, everybody needs that. So, and when you find patients who have advanced fibrosis or cirrhosis, then that's where we do recommend that they get the surveillance tests for liver cancer. And as I mentioned earlier,

we still do that even after they've been cured of hepatitis C. If they had cirrhosis or advanced fibrosis before they were cured of their hepatitis C, they still have this risk. It's reduced, but they still have this risk, so we recommend surveillance.

One of the questions that comes up a lot is do you really do everybody with bridging fibrosis who doesn't have cirrhosis? And I'm generally broad in that recommendation and do recommend that to my patients, partly because I know that our tests are not perfect. I know that there's some degree of variability in the tests so that a patient with advanced fibrosis on my test might really have cirrhosis and my patient with cirrhosis might really have advanced fibrosis. These tests are not perfect, so I'm a little bit cautious. Again, I make this shared decision-making with the patients. For some, this is really tough. For some, this is really expensive and so I don't want this to become a burden to them but I want them to understand how we've done a great thing by curing their hepatitis C; we've lowered their risk of liver cancer, but there is this residual risk and this is how they could handle it.

Dr. Lim:
This is a really important point because I think what you've very clearly articulated is that for patients with hepatitis C cirrhosis, there's a very strong indication for routine liver cancer surveillance life-long, even after SVR. However, for those patients with advanced fibrosis, it sounds like there is much more nuance where there still is a risk – perhaps a lower risk – and so I certainly, similar to yourself, do advise consideration of liver cancer screening with a F3, particularly because we're not using biopsies anymore and there's a fear that we're missing some early cirrhotic patients who are actually at increased risk because we just use inferior non-invasive tests. David, how do you approach that? Do you screen only the cirrhotic patients? Or do you also screen those with F3 or greater?

Dr. Bernstein:
No, so with hepatitis C, we screen everyone who's F3 or greater, just like the two of you. I think the other important point that Andy alluded to in using transient elastography or FibroScan, you know, many times we repeat these after the patients are cured and the patients want to continually have them done every year or every couple of years. And we do see regression of fibrosis stage from F4 to F3 or F2, even lower but we still – and I'd love to hear everyone else's opinion – we still screen the patients continually after cure if they had bridging fibrosis or cirrhosis on their pretreatment FibroScan, transient elastography.

Dr. Lim:
We really don't have the evidence to know that that risk has gone away, as you're suggesting. So, I agree.

Dr. Bernstein:
I think it is an important point to get out there for folks.

Dr. Muir:
Agreed.

Dr. Lim:
Yes, and I think that's really important that there are studies which show that patients with pretreatment cirrhosis, their FibroScan scores may go down to the equivalent of CH1 or 2 but the biopsy still shows cirrhosis and they still bear a risk of cancer. I think that although I also do, on occasion, check non-invasive tests post-SVR, although that can be useful for clinical management, that shouldn't eliminate or halt the recommendation for liver cancer screening. I do want to ask another question as to the choice of imaging modality. I know that ultrasound is only recommended by the AASLD for routine liver cancer surveillance and so the question for the two of you, in which patients would you consider the use of CT scan or MRI, and how you broach that with patients and with payers?

Dr. Bernstein:
Sure, I'll start. We use ultrasound most of the time in our patients, especially those with hepatitis B because the population we see actually tends to be a thinner population with hepatitis B than hepatitis C. We use CT or MRI as a primary screening modality in those patients that are significantly overweight, in those patients that have decompensated cirrhosis. Those are really the two main categories that we would use. We haven't had a lot of pushback from payers. Most of the time we're able to get on the phone with the payer and get that approved, but the vast majority of our screenings are really done with ultrasound. We pick and choose where we have the ultrasound done and it's important to know who's doing the ultrasound and have a relationship with that radiologist because the quality of ultrasound can vary significantly across various institutions.

Dr. Muir:
Our experience has been very similar. We actually hear from our radiologist if it's a good quality ultrasound, if they feel like they can see it. And if they cannot, then that's where we move to the other modalities. I tend to favor MRI if I can for my younger and middle-aged patients because otherwise, we're talking about a lot of radiation over many years with CT scan and similar to how David described. I've actually found that we've been successful in getting those covered when we've taken that reasonable approach.

Dr. Lim:

So, I think it's pretty clear that there are certain patients where ultrasound may be appropriate but there are some patients, particularly those where ultrasound may have inadequate visualization, that CT scan and/or MRI may be appropriate and generally are accessible for our patients. So, with this, I'd like to go ahead and close and want to offer each of you an opportunity to share any final lessons learned or clinical lessons with our clinician audience. I'll start with Dr. Bernstein.

Dr. Bernstein:
Sure, so I'm going to keep my comments to hepatitis B, since I've discussed that mostly. And I think some important points to remember—hepatitis B is a chronic disease that we can't cure. Antiviral therapies can significantly improve the degree of fibrosis and prevent or delay the development of cirrhosis or liver cancer but it never eliminates it. And while there are many risk factors that increase the risk of developing primary liver cancer in hepatitis B, it's important to remember that everyone with hepatitis B should be screened, usually at an interval of every 6 months with ultrasound and probably an alpha-fetoprotein. If people stick to that method, we're not going to miss things and it'll give the patients, a better opportunity should they develop hepatocellular carcinoma to be treated appropriately.

Dr. Lim:
Fantastic.Dr. Muir, any final lessons learned or clinical lessons?

Dr. Muir:
I still think the key to having an impact around liver cancer is to identify patients with liver disease early. We still have patients who show up – I had one this week with a new diagnosis of widespread liver cancer and I'm making the diagnosis of hepatitis C in the patient at that point. This was a Baby Boomer. This was someone who could've been found. We have not done effective screening for hepatitis B and C. If we did that better, we have the drugs we talked about, we have the modalities to avoid this. We just need to be better with our screening programs to find our patients with hepatitis B and C.

Dr. Lim:
I think that is an important reminder for all of us that screening recommendations for hepatitis C have evolved from the CDC and the US Preventive Services Task Force for screening all adults age 18 or older, and in pregnant women. I think that we have a long way to go before we can achieve that goal, but it's going to be critical if we're going to make an impact on the overall burden of hepatitis B and C and liver cancer. And so, with that we'll close. I'd like to thank again our expert panelists, Dr. Bernstein and Dr. Muir. Thank you again for your attention.

Dr. Bernstein:
Thank you, Joe, for having us.

Dr. Muir:
Thank you.

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