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Assessing New Guidelines for Hepatocellular Carcinoma

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. And today we are joined by Dr. Amit Singal, who will be discussing the new guidelines for hepatocellular carcinoma, or HCC for short. Dr. Singal is a Professor of Medicine and the Chief of Hepatology at the University of Texas Southwestern Medical Center in Dallas.

Dr. Singal, welcome to the program.

Dr. Singal:
Thanks, Dr. Buch, for having me. I'm very excited to be here.

Dr. Buch:
To start us off, Dr. Singal, should we be utilizing modalities other than standard ultrasound for routine early detection of hepatocellular carcinoma in cirrhotic patients?

Dr. Singal:
Well, Dr. Buch, it's a great question, and this has been an area of debate for many years. The first thing that I think people have to remember is that screening for HCC is very important in patients with cirrhosis. There have been several studies that have shown a strong association between screening and improved clinical outcomes, including reducing cancer-related mortality. Now how we perform screening has been once again an area of debate. There have been guidelines in the past that have recommended abdominal ultrasound alone, but more and more data have shown that ultrasound alone has insufficient sensitivity to find HCC at an early stage, missing over one-third of tumors at an early stage. So there have been increasing interest in adjunct biomarkers that can be used with ultrasound, and the one that has been best validated is alpha-fetoprotein, in short AFP. Several studies have shown that when you use ultrasound and AFP in combination, you significantly increase sensitivity for early HCC detection, and this is offset only by a small decrease in specificity, so the overall accuracy of the two tests in combination is higher, and that's why the most recent guidelines will now advocate for using ultrasound and AFP every six months for our screening modality in patients with cirrhosis.

Dr. Buch:
That's great, but you probably do a lot of conferences, as I do as well, and if you have your audience raise their hand, especially the primary care audience about who is good with doing that ultrasound every six months, you'll see that there are very few people who are doing that on a regular basis. How do we address that in the general medical population?

Dr. Singal:
Dr. Buch, very important question. When you take a look at the studies that have looked at screening utilization, you see that less than one in four patients with cirrhosis receive screening at a regular six-month interval, and this has been an area of much research over the last couple of years in terms of evaluating relatively "simple" interventions, primary care education, patient education, our favorite best

practice alerts that can be built into our electronic medical records, and even more complex interventions, like mailed outreach strategies, where you identify all patients with cirrhosis and mail them invitations to get screening at regular intervals. The good thing is that each of those interventions has been shown to be efficacious, increasing screening utilization; and one of the other changes in the guidelines is that we now advocate for studies to see how we can effectively implement those interventions as part of routine care.

One of the other things that we're trying to do as a larger community is to find blood-based biomarkers that would have sufficient accuracy if they were used alone. We're just getting ready to launch actually, a large, randomized trial of ultrasound versus biomarker-based screening. And if those emerging biomarkers are sufficiently validated, this would not only potentially increase sensitivity for early cancer detection but also make it easier for us to implement this, thereby increasing utilization and adherence.

Dr. Buch:
That's great to know. Let's hone in now on alpha-fetoprotein and what can cause false-positive or false-negative alpha-fetoprotein blood test results.

Dr. Singal:
AFP has been one that has been much maligned given insufficient accuracy when used alone, and so we do recognize that, as you mentioned, you can have both false-positives or false-negatives. So false-positives we typically see with patients who have underlying hepatic inflammation, so most commonly in the setting of active viral hepatitis whether related to hepatitis B or hepatitis C. The good news is that we have very effective medications now. We have very effective antivirals that can suppress hepatitis B, and we have a cure for hepatitis C. And when those patients are treated for their viral hepatitis, you reduce the hepatic inflammation, and you reduce the likelihood of seeing false-positive AFP levels.

Conversely, false-negatives do occur with AFP as well. We know that about 40 to 50 percent of HCC can actually have normal AFP levels until quite advanced stages, and so this is unfortunately, one of the limitations of using AFP alone. That being said, the guidelines don't recommend AFP alone. They really recommend this as an adjunct to ultrasound. And so despite this risk of false-positives and false-negatives, we really do find that it is additive when using it in combination with abdominal ultrasound.

Dr. Buch:
So which patients should be considered for surgical or ablative therapy?

Dr. Singal:
The main goal of HCC screening is to find patients at an early stage because this is when you can give curative therapies. And our curative therapies involve surgical therapies, for example surgical resection or liver transplantation, and if somebody isn't eligible for surgical therapies, then you can use local ablation. The reason why we want to deliver those therapies is because this offers very high complete response rates in 95 to 99 percent of patients and is associated with the longest survival, so median survival is well over five years if not over 10 years with most of these therapies. This is quite a complex topic in terms of when you can give these different surgical therapies or local ablative therapies, but I think in general we think of these as the main therapies that we have for early-stage disease; surgical resection if you have good liver function and early-stage disease liver transplantation if you have liver dysfunction, for example decompensated cirrhosis or portal hypertension, and early-stage HCC. And then local ablation if you have early-stage disease and are not eligible for surgical therapies.

Dr. Buch:
That's great. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Amit Singal about hepatocellular carcinoma, or HCC, in cirrhotic patients.

Now, Dr. Singal, should patients with cirrhosis and HCC that have been successfully resected or ablated undergo adjuvant chemotherapy?

Dr. Singal:

Dr. Buch, this is such a timely question because this has been an area of need for the field for several years. So one of the issues with local ablation and surgical resection is that it has a very high recurrence rate. So we just discussed that these are great therapies because they offer complete response and long-term survival, but the issue is that they're also associated with five-year recurrence rates somewhere around 50 percent if not higher. And so there has been a lot of interest in what we can do to reduce that risk of recurrence. And prior studies for adjuvant therapy have unfortunately, largely failed to show any benefit until the trial that just reported out earlier this year. So the first positive adjuvant trial in HCC was reported earlier this year showing a benefit of using the combination atezolizumab and bevacizumab, so that's an immunotherapy agent in combination with a VEGF inhibitor, and you use this in high-risk patients, and you significantly improve progression-free survival. Now all we have right now is a press release from the company. We're still awaiting those data to be presented in full form, and we anticipate those data being presented in April of this year, but it's a huge win for the field that we finally have a therapy that successfully improves progression-free survival after ablation or surgical resection in high-risk patients.

Dr. Buch:
And continuing on this theme, which patients with cirrhosis and HCC awaiting liver transplant should receive treatment?

Dr. Singal:
So we discussed also liver transplantation, an incredible curative procedure for patients with underlying liver dysfunction and early-stage HCC, that offers cure for the cancer, offers cure for the cirrhosis, but unfortunately, one of the issues with liver transplantation is the gap between the number of people who need a liver transplant and the number of organs available; so this unfortunately, often results in prolonged wait times on the waiting list, and so we have to treat that tumor while we are waiting for that liver transplant to occur. And now for most of the areas of the country, you see waiting times at least six months if not longer, and so we treat those patients with local therapies to control the cancer while waiting for the liver transplant. One of the things that we continue to need to do is encourage our patients, our friends, ourselves to be donors because we really need to improve outcomes for cirrhosis, as well as HCC so hopefully, if we can increase organs, we'll be able to save more and more lives in the future.

Dr. Buch:
Perfect. Before we conclude, Dr. Singal, are there any other thoughts you'd like to share with our audience today?

Dr. Singal:
First, to reinforce the fact that screening is very important. This is really one of the main things that we can do as a medical community to improve HCC outcomes. This remains one of the few cancers in the United States that has an increasing mortality rate, and so we really need to do better in finding this cancer at an early stage when we can deliver curative therapies. And the other thing that I'd say is when we find these people with HCC, it's critical that we refer them for multidisciplinary evaluation, preferably in centers that can consider liver transplantation as a potential therapy for your patient. There have been several studies that show patients seen in large expert centers with multidisciplinary care that have significantly improved outcomes, including improved survival compared to patients seen elsewhere. And I think it's always the hardest day in clinic when I see a patient with HCC who wasn't seen in one of those centers and was initially eligible for a curative therapy and instead received noncurative therapies, and by the time they get to us, that window is unfortunately, closed. So screening is important and a referral to multidisciplinary settings where liver transplantation is considered if you have somebody who's diagnosed with HCC.

Dr. Buch:
What an outstanding review of HCC. I want to thank my guest, Dr. Amit Singal, for sharing his insights.

Dr. Singal, thanks so very much for joining us today.

Dr. Singal:
It was really a pleasure to talk about this and thanks so much.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening, and see you next time.