Ultrasound elastography can save patients from invasive procedures and bring radiologists to forefront of diagnosing diffuse liver disease.

Last month, a consensus conference statement was published in Radiology by the Society of Radiologists in Ultrasound recommending that elastography techniques can be used to distinguish patients with no or minimal liver fibrosis and differentiate them from patients with severe fibrosis or cirrhosis. There were two significant outcomes from this recommendation: patients no longer need invasive liver biopsies to diagnose liver fibrosis, and radiologists will play a huge role in diagnosing diffuse liver disease, a part they did not play before.

Diagnostic Imaging spoke with lead author Richard Barr, MD, PhD, of the department of radiology, Northeastern Ohio Medical University in Rootstown, about what radiologists need to know about this technique.

Diagnostic Imaging: What’s some background on liver disease?
Barr: Liver disease is a substantial worldwide problem. It can be caused by several different ideologies: hepatitis B, hepatitis C, alcoholic liver disease, biliary cirrhosis, or nonalcoholic static liver disease. All of these ideologies tend to have one final pathway: they all cause chronic diffuse liver disease that leads to fibrosis and progresses into cirrhosis. It then becomes complicated cirrhosis, which has a relatively high risk of mortality.

The CDC estimates there are 240 million people worldwide with chronic hepatitis B, with an estimated 1.2 million in the United States.; hepatitis C has a prevalence of an estimated 2.7 million in the United States, and between 130 and 150 million worldwide.

In North America, diffuse fatty liver disease is the problem. Nonalcoholic fatty liver disease (NAFLD) has an estimated prevalence of 27%-34% of the US population, according to the Radiology study. Fatty liver disease, by itself, is not too much of an issue but it can progress to nonalcoholic steatohepatitis (NASH) in about 10%-20% of these patients. NASH is where the liver becomes fibrotic and will progress to cirrhosis. So we are talking about a huge population of patients with a diverse number of ideologies, but all with the end result of having cirrhosis.
What are the challenges of diagnosis, management, and treatment of cirrhosis?

Fibrosis is often not picked up until the patient presents with cirrhosis. So we often don’t pick these patients up until far within the progression of the disease. There has been a significant change in the medical community because, at least now for hepatitis C and on the horizon for hepatitis B and NAFLD, there are treatments. Ideally, these treatments work better when we are picking up the diagnoses at a relatively early stage, so having a technique that would be able to diagnose the mild-to-moderate degrees of fibrosis would allow that patient to be treated appropriately sooner, or at least flagged to their doctors so they know to treat the patient and, again, the goal is not to let them get to the point of cirrhosis.

I think it’s important to note that in the past, the diagnosis was made by a liver biopsy, and obviously a liver biopsy is invasive; there is a small risk of death. It’s a painful procedure, and it really is not a good gold standard because these processes are very diffuse and a liver biopsy only samples a small portion of the liver. So it’s not the perfect test and the other problem is, as we are using these new treatments, we are finding that the treatments can reverse the degree of fibrosis. Ideally, we’d like to be able to monitor patients to see if these drugs are improving or decreasing the amount of fibrosis. The treatments are extremely expensive so being able to monitor the treatment is very important. Insurance companies are concerned about the high cost and making sure the treatment is given appropriately to the appropriate people.

This is where the elastography enters in. The elastography is an ultrasound technique where we use a stress, if you will. In the case of shear wave imaging, we use a low-frequency, high-energy pulse that in a sense “pushes” the liver. We use that ultrasound beam to push the liver and it creates shear waves. You can think of this like when you drop a stone in water, you get ripples, so the stone is that ARFI push pulse and the ripples are the shear waves, and the shear waves travel through tissue based on its stiffness: the softer the tissue, the slower the shear wave speed, the harder the tissue the faster the shear wave speed.

This technology could be used on multiple different organs, but it’s really a very good technique for the liver. We can do shear wave imaging, calculate out the shear wave speed through the liver, and then use that to identify the stiffness of the liver. There have been multiple studies done by vendors with various different techniques which show that this does work, the technology has been available in Europe and Asia for several years and I think it’s fair to say that the number of liver biopsies done in Europe and Asia have decreased dramatically.

The UK government actually put out a statement, the NICE guidelines, in which it recommends that liver biopsies not be done for diffuse liver disease and that elastography be the first method of choice. Liver biopsies would be reserved only if there is a specific reason why you would need to
have a biopsy, for example the elastography does not match the clinical picture or additional information is needed that's not provided by the elastography. In talking to my colleagues in Europe, liver biopsy for diffuse liver disease is becoming a rare procedure. This technology is newly approved in the United States and we suspect the same thing is going to happen here.

**So imaging is new to the role of diagnosing liver disease?**

In the past, the problem was conventional ultrasound, without elastography was very poor at determining if there was fibrosis in the liver. If you got to the point of cirrhosis, it was reasonably good at characterizing cirrhosis but again it was not very good at those lower levels. Ideally, it would be nice to 1) pick up those patients to make a diagnosis and intervene early to prevent it from progressing and 2) start them on a treatment if the etiology is treatable to reverse the fibrosis. Other things like MR are not that sensitive without elastography in determining these low to intermediate grades of fibrosis. It is reasonably good at picking up cirrhosis, but we would like to pick up these patients before they get to the end stage of cirrhosis. CT is awful for very low sensitivities, again, until you get to the very end stage of disease. So conventional imaging, CT, MR, ultrasound, are not very good at diagnosing the disease until it was in its very end stage.

**If radiologists were already using imaging to diagnose focal disease, is diffuse liver disease a new area for them?**

Definitely, and the European and Asian radiologists had the technology approved several years ago so they are a little bit ahead in incorporating this into their practice. I think in Europe and Asia, there are a lot of hepatologists and internal medicine doctors that do their own imaging so I think it’s being embraced there not only by the radiologists, but by other people that work with liver disease. The imaging component is extremely important. As these patients go from mild to moderate to severe fibrosis and then to cirrhosis, as they progress along that continuum of disease, their risk for hepatocellular carcinoma (HCC) increases significantly. One of the things that I think most radiologists are very familiar with is patients that are diagnosed with cirrhosis especially from hepatitis C, get an ultrasound every six months to screen for hepatocellular carcinoma, so again we are doing the ultrasound to look for the complications of cirrhosis, but now with the elastography it’s allowing us to pick up the patients earlier.

I think right now radiologists are looking for gallstones, masses, and HCC in the average patient and we are doing screenings for HCCs in the patients that have known cirrhosis. But now with this technology, we are really adding additional clinical information that is very important. We can flag these patients that have these diseases that may not be known. There was a study in Romania that just screened everybody that came in for abdominal ultrasound for whatever cause, abdominal pain, abnormal liver function tests, etc. and they found that about 30% of the patients they screened that didn’t suspect to have cirrhosis actually had some degree of fibrosis that was significant and those patients needed follow up. So we are flagging these patients earlier so they can be provided appropriate treatment and hopefully prevent them from getting to cirrhosis.

There are other things that we can do now with imaging: we can add Doppler, we can evaluate to see if these patients move to cirrhosis, we can monitor the complications (verices, portal vein thrombosis, a big spleen). All of these things we can now pick up with ultrasound, so we can tell the clinician or hepatologist for the most part where this patient is on this continuum of being normal to mild to moderate to severe disease to cirrhosis and then decompensated cirrhosis. That’s really critical information to the hepatologist for how to treat that patient and to provide follow up to see if the patient is getting worse or better with treatment.

We are finding patients that clinically are not suspected of having fibrosis, so their clinician would not have ordered a liver biopsy and we are picking up patients that would not have been flagged to get a liver biopsy until they were farther down the path of getting cirrhosis.

**Has there been a lot of interest in elastography?**

I think that there is a very high interest in this. I get calls and e-mails daily from people. One of the things about ultrasound elastography is the technique is very critical to give good results and there are a lot of people asking us for our protocols and how we’re doing this to make sure they get accurate results. I think there is a huge demand and interest in using this technology. There are also a huge number of patients that this technology would be helpful for. I think the technique is actually very easy and very simple; the problem is there are a lot of little pitfalls. In a sense, there is a learning curve to do this. It’s not a difficult thing to do, but there are a lot of possible errors in getting the measurement, so training on how to do the measurements exactly and where to do the measurement is really critical for getting good results.

**How are radiologists trained?**

Each vendor has the responsibility of making sure that if they sell the system to someone, that they...
get trained. We are in the process of developing a hands-on course with Philips that will allow physicians to get hands-on training. Sometimes it’s hard to train radiologists with just words on paper, so I think that education and training is very critical to get people on the right path. At this point, there really are no guidelines or standards as to how many cases someone should do to get used to the technique. I think people are struggling because as the technology comes out, there is greater demand for education so I suspect that there now will be organizations that will start offering hands-on courses for training.

**What are the limitations?**

There are some technical factors. The examination has to be approached through the ribs. We have to take the measurements at least 1.5 cm below the liver capsule and the probe has to be perpendicular to the liver capsule. We have to avoid blood vessels and any lesions when we are doing the measurement. Right now, I think most people are recommending you do 10 measurements in a similar location and then take the median of that measurement to get a more accurate measurement assessment. Then there are things like the standard deviation or the interquartile ratio, which is another way of looking at the standard deviation, and is important to make sure you have a good cluster of measurements around that median and that you aren’t getting measurements that are widely varied.

This technology looks at liver stiffness and if you’ve got chronic liver disease, then it’s really correlated with fibrosis. If you’ve got acute liver disease or chronic liver disease with acute exacerbation, then we are looking at stiffness from the fibrosis as well as the inflammation from the acute process. So in those situations, comparing it to liver enzymes to realize that those measurements are not providing you the fibrosis, but a combination of fibrosis and inflammation is another important factor that people need to be aware of. I think with larger patients, it is a little more difficult because the thicker the subcutaneous fat, the more likely it is that the sound waves are not getting through to generate the shear waves.

**It seems to be a great diagnostic tool, what is its role in management of disease?**

I think we are moving toward using it for management because the FDA has approved drugs for treatment of hepatitis C. I believe approval of drugs for hepatitis B are on the horizon, and there are going to be drugs approved for fatty liver disease. For all of these drugs, we need to know when is the appropriate time to use them because they are all very expensive. How do you select the patients that would qualify for this treatment? I believe that some insurance companies actually now for hepatitis C are requiring that the patient has to have a specific stiffness value or higher before they will approve payment for the treatment. I think we’re still working this out because it’s relatively new technology that you can monitor the patient with treatment to see if you’ve halted the disease, improved the disease so that the fibrosis is resolving, or to see if the patient is still progressing and you know that the treatment is not working.

The NICE document from the United Kingdom actually did a cost analysis and they figured there was a huge cost savings in using this technology versus doing liver biopsies.

I’ve talked to people on the CPT committee and there is an approval for a shear wave elastography measurement, but you can’t do imaging on the same day. So you could use that code, but then you could not bill for doing the imaging part and, in general, the reimbursement for doing the imaging is greater than the elastography, so my suspicion is, at this point, the radiologist would rather do an imaging study and add in the elastography using that nonreimbursable code. It doesn’t really make sense to have the patient come back on two different days to complete the exam, although you would think the CPT code committee would have considered that.

But there is a big push to now address the CPT code so that we can do both on the same day.

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