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Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it’s a conversation about liver cancer with Doctor Stacy Stein.

Doctor Stein is an associate professor of internal medicine in medical oncology at the Yale School of Medicine, where doctor Chagpar is a professor of surgical oncology. So Stacy, we don’t know a whole lot about liver cancers. We certainly talk a lot about breast cancer and colon cancers, but tell us a little bit more about how we think about liver cancers.

Yeah, you’re right. I don’t think it gets the same attention as some other cancers in the public.
But I think it’s a really important cancer to talk about because it’s actually one of the few cancers that is still on the rise in our country. Some people might be familiar with some of the traditional causes of cirrhosis which causes liver cancer. Worldwide this is a very prevalent cancer, especially because of hepatitis B and mother’s passing it on to their babies. In the United States, we see more people that have developed cirrhosis from hepatitis C or alcohol use, but another cause is actually on the rise in the United States that we don’t talk about a lot and that is something called NASH Cirrhosis, which is related to the obesity epidemic, and we’re seeing that more commonly now and I think it’s something important that people are more aware of and primary care physicians are more aware of, to screen their patients. How exactly do they do that and is there screening for it? And if so, what is that? Often you know
who is at risk for those kind of factors, so it’s people that are older that may have obesity, high blood pressure, diabetes, right? So a lot of these common diagnosis that travel together and then you know it’s also not uncommon for people with all these diagnosis to be on several medications, and then they may have blood work where their liver enzymes are a little bit out of range, but I think it usually gets ascribed to maybe a side effect of one of the medications that they were on instead of thinking about underlying liver disease and so it’s important when we see elevations in liver enzymes to be thinking that this might be a primary liver issue. Interesting, and because we’ve talked on this show so much and on others about how there really is this obesity epidemic and over 40% some people even say over 50% of our population are overweight or obese, how often should you be getting those liver enzymes checked?
And if they are abnormal, what should ensue? Yeah, that’s a good question, so I think the screening needs to be updated. You know most of the screening and efforts in the hepatology guidelines really focus around, which is still very important, screening people for hepatitis B and hepatitis C because we have treatment now for hepatitis C. We have treatment for not curatives, but we have suppressive treatment for hepatitis B. And the question is then who should we be screening for this NASH Cirrhosis? You know the guidelines are not completely set the same way as they are for these other causes, but I think certainly when you see someone that’s having elevated liver enzymes or potentially decreased platelets, that could be a sign. And portal hypertension, or people have had imaging for other reasons and you find changes that are consistent with cirrhosis. I think it’s important to really go down the path of fully working that up. But I don’t think the guidelines are really clear yet of how we
screen for NASH Cirrhosis.

But I think it’s going to be important to give better direction to people in primary care about that.

You mentioned that there’s good screening for hepatitis B and C, and certainly we have vaccines for both of those, but let’s talk a little bit about how we screen for those HEPAs as well.

I mean, should that be something that is routine at your doctor’s office.

How frequently should that happen?

Or is that something that you only screen for if you’re at risk of getting those hepatitides.

And what are those risk factors?

In the United States, all babies are given a series of hepatitis B vaccines, so it’s really more of an issue of screening people that were not born in this country, especially Asian populations.

Where the numbers are the highest.

For hepatitis C, it’s recommended that especially everyone from the baby boomer generation is screened at least once, and then certainly you know if there’s any concern for a more acute liver process, that could be repeated.

There are initiatives
through primary care, especially through the VA system. Unfortunately, there’s a large burden of hepatitis C to really make sure that everyone is screened at least once, because we do have treatment now, which is important to know and make sure that’s started in a timely fashion. And screening is a routine blood test, so if you haven’t had a blood test and are in that baby Boomer generation, or you have been born in another country, it’s a good idea to at least get checked and see if you have one of these two hepatitides which may put you at risk of developing liver cancer. So let’s talk a little bit about that next step when you were talking about how if your liver enzymes are elevated that should really spur people on to thinking about liver cancer as a potential cause for that, so aside from an abnormal blood test of your liver enzymes being elevated, are there other symptoms that people should be looking for in terms of liver cancer or can it be...
completely asymptomatic?

That’s a good question.

So what’s so interesting about liver cancer is that it’s so tied to Cirrhosis and underlying liver disease, and so those two things obviously are separate but also very related.

So you know the symptoms of the cancer may not be traditional symptoms. People think about, we don’t have a lot of nerve endings inside the liver. So often people don’t feel a difference necessarily the way someone might feel a mass somewhere else in their body. And unless there’s really tumor pressing on the capsule of the liver where there are a lot of nerve endings, they probably won’t feel any different.

So a lot of the screening really winds up being identifying the people at risk of for Cirrhosis and identifying cirrhosis and then looking at that group and screening them with imaging for liver cancer.

Because we know that the cure rate and the success at treatment is better the earlier we can find it.

So for patients that present with a single liver lesion and they have good liver function,
they could be candidates for surgery where the tumor is able to be removed. For some patients who have still pretty limited disease and they may also have some cirrhosis, or declining liver function, and there's a lot of rules surrounding this, but they could potentially be candidates for liver transplant and that could also be a curative option, but if the cancer is found later, then we don’t have those kind of options and we have to then think about other treatments.

So it’s important to find it at an early stage as with so many cancers. You may be feeling completely asymptomatic. You hear this on the radio and you decide to go and see your doctor because maybe you are overweight. Or maybe you have a history of alcohol in the past and are worried about cirrhosis or maybe you’ve been screened for hepatitis B or C and your doctor does that screening test and says, your liver function studies are a little bit abnormal. So imaging is the next thing that you should
expect in order to try to find a liver cancer early, right?
So there's a few ways to image the liver, so sometimes for screening they start with just an ultrasound, which is pretty easy to get, noninvasive.

There's a probe that is put over the abdomen and is kind of pushed down, and then there's images that show up, and they could often find changes of Cirrhosis and possible tumor.

And when we're really concerned that there is cancer, and we best want to characterize it, the best imaging, what's considered the gold standard is really an MRI for patients that are not able to get an MRI for one reason or another, we're able to do a CAT scan with something called triphasic imaging, where we're able to get a very good look at the liver also so most patients once there's any real concern, they usually getting an MRI, and if not a CAT scan and so what's the next step? A biopsy now?

That's an excellent question.
You know, for every cancer, I think most patients would identify a biopsy as being the next step, right? So if we have imaging that’s concerning, typically as oncologists, we always order a biopsy for cancers and that really gives us the definitive answer. Interestingly in the history of liver cancer imaging has been so good at looking at specific characteristics of the cancer that traditionally you have not needed a biopsy to identify each HCC or hepatocellular carcinoma, and we’ve been challenging that a little bit more recently because there’s a lot of caveats where you could have mixed tumors of bile duct cancers with HCC. Or you know, as tumor profiling is becoming more commonly used, we really like to have tissue biopsy so that we could do these molecular tests, and so it has become more common to have a biopsy before we start treatment. But I would say historically a lot of patients wind up getting treated for liver cancer in the absence of a biopsy, which is definitely unusual as compared to other cancers. And I guess the other thing that is unique about the liver or somewhat unique is
that it’s a good place for cancers that start in other places to go not just as a place for cancers to arise. How can you tell the difference between a primary liver cancer that starts and grows in the liver, often in a cirrhotic liver, versus a cancer that started somewhere else, say in the colon or somewhere else and goes to the liver.

And so that’s always the first question. When you see a mass in the liver, did it start there or did it spread there from somewhere else so the imaging does help with that.

If you do what’s called this triphasic imaging, when the contrast is injected into someone, they look at certain phases. So that the liver has two blood supplies, there’s a blood supply from arteries and from veins so the liver is unique in that way and there’s kind of a characteristic appearance that is different between metastases and liver cancer.

But that being said, sometimes the imaging is not as clear and you don’t feel confident and that’s really where a biopsy is
And so once you get that biopsy, you can figure out if this is a primary cancer or a secondary cancer. Hopefully, this will give you a little bit more information to help you treat it.

Liver cancer can occur as a single tumor, which is what happens in most cancers, right? Most cancers start out as a single tumor and then can spread. Sometimes, liver cancer is called multifocal disease, meaning that it’s not really one area that spread to other areas. But because of the cirrhosis, you could think of the whole liver as being at risk for developing a tumor. If you’re at risk for developing tumor, it’s important to monitor your liver regularly.

Well, we’re going to dig into all kinds of aspects in terms of the qualities of tumors in the liver and how we go about treating them right after we take a short break for a medical minute.
Please stay tuned to learn more about liver cancer with my guest Doctor Stacey Stein. Support for Yale Cancer Answers comes from AstraZeneca, providing important treatment options for various types and stages of cancer. More information at astrazeneca-us.com.

This is a medical minute about head and neck cancers, although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway to test innovative new treatments for head and neck cancers, and in many cases less radical surgeries are able to preserve nerves, arteries and muscles in the neck, enabling patients to move, speak, breathe, and eat normally after surgery. More information is available at yalecancercenter.org.

You’re listening to Connecticut public radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by
my guest doctor Stacy Stein.

We’re talking about GI cancers in particular liver cancer, and right before the break we talked a little bit about all of the risk factors that can really put you at risk of developing primary liver cancer, which can be an isolated event, or it could be multi focal. So Stacy, when we talk about liver cancers, how often are these found as a single spot in the liver versus more extensive disease?

That’s a good question, so I think it really depends on which group of people you’re looking at. For patients who have known that they have underlying risk factors and they’ve been getting screens, they are much more likely to be found with early disease. But I would say, unfortunately, I see patients all the time who present with much more advanced disease. Because you they either were not being followed by anyone, or they didn’t realize that they had cirrhosis and so they could be found with disease that’s already
not eligible for surgery or transplant. The disease may have metastasized already, and so we certainly see people that have either presented with disease very late or after treatment. For early disease, the disease has progressed and as we talked about before the break, I mean certainly it’s always better if you can find cancer early when it’s most treatable and when either surgery or local therapies are an option to get rid of the primary cancer. But when that cancer is locally advanced or even metastatic when it spread and those local therapies are no longer an option, we still have options to treat these patients. And that’s really the area that I’ve been most focused in. I’m very lucky at Yale to have a fantastic multidisciplinary liver team and I just want to mention we actually meet weekly. We have our own separate conference just for liver cancer and there’s such a great group of people. We work with the surgeons, the transplant surgeons, the hepatologist,
the Interventional radiologist.

There’s Oncologists.

We really have a great group that focuses on all aspects of treatment.

My focus as an oncologist is really more in patients who are not candidates for these curative intent treatments like transplant or surgery.

For patients with local disease where the disease is still confined to the liver and there’s not more than a few separate tumors that Interventional radiologists have really played a large role in treating those patients, and they treat with a wide variety of modalities where they could apply some chemotherapy or heat or cold, or they do ablation techniques, and then at some point either because someone is developing more tumors or if there’s any metastatic disease, meaning tumor has left the liver, then we really focus on what we call systemic therapies. So either the treatment is a pill form or intravenous form, but then the drugs are absorbed in the body and go everywhere, and I have to say over the time that I’ve been at Yale, in the last 10 years,
we have made tremendous strides in the last few years and having more treatment options that are more effective for liver cancer, so that’s been really exciting. So tell us more about those developments. I mean for many people the concept of chemotherapy is really scary, but you mentioned that some therapies that you give actually can be oral. The first drug that actually showed a benefit in helping people live longer with liver cancer is a drug called sorafenib and that’s actually a pill form of treatment. It’s not really traditional chemotherapy, we call them tyrosine kinase inhibitors. While sorafenib had some benefit, we all recognize that it wasn’t enough. And then if patients didn’t really tolerate it, their cancer started to grow again. You know there were many years where we really didn’t have other good treatment options. And then in the last few years there’s been a lot of success in both finding more of these tyrosine kinase inhibitors that are more effective potentially.
and then the other area that’s been really exciting has been the use of immune therapy in liver cancer, so I want to dig into both of those kind of arms of the equation first. You know when we talk about tyrosine kinase inhibitors sometimes that’s very similar to what we talk about in breast cancer. For example, many of our listeners may know about HER2 and the fact that we can have a targeted agent against HER2 that can be very effective. So with these tyrosine kinase inhibitors in liver cancer, are there particular receptors that you’re going after?

So are there markers that you can look at a cancer and say, ah, ha, Mrs Jones has this particular receptor and has this particular receptor and I have a drug that can target. Yeah, that’s a really good question and there’s a few things that you asked that I want to address and one is do we have a biomarker? Which really means is there some way from the patient that I’m treating
either from their blood work or something from there from their biopsy that I could identify that would predict whether they would respond to treatment or not, and unfortunately the answer is we really don't have a biomarker for liver cancer the way that we could test HER2 expression in breast cancer, or other cancers and say this drug is more likely to work. We do follow something called the AFP. The Alpha fetal protein and in about 80% of liver cancers that protein is made and so the value of it and it going up or down gives you a sense of response, but it doesn’t actually predict what drug he would respond to if there is a real need for finding a biomarker that would predict response to any particular drug, but the truth is, we don’t have one, and so we really are giving these drugs without really knowing who it is that is going to respond or not, and we’re trying sequences of drugs. I wish we did have a biomarker. There’s a lot of interest in
developing one when you ask what target are we hitting with this tyrosine kinase approach, the truth is these are what we call dirty tyrosine kinases, meaning they don’t target just one protein, so one of the proteins they target is something called veg F. The vascular endothelial growth factor which is involved in blood vessel formation for the tumors. We do know that that’s an important target for liver cancer, but it’s not the only one that’s targeted by these drugs, so there’s other pathways that are being targeted and they probably have some role in the benefit of these drugs too. And you know, there’s still a lot more to really understand about how these drugs work in this cancer. It would be nicer if you could biopsy a tumor and say, this tumor has a very high veg F level and you have a specific drug that would target that and Voila, the cancer magically disappears, but I guess we’re a bit far off from that. And what’s interesting too is
that in immune therapy
there’s been so many recent
studies looking at the role
of different immune therapy,
drugs, and liver cancer,
and even then for a lot of
cancers you could check something
called the PDL one expression,
and by looking at the number
of immune cells infiltrating,
in the tumor on the biopsy,
you could have some kind of
sense of prediction of how likely it is
someone would respond to immunotherapy,
but even that for liver cancer
has been very unreliable.
The expression of that protein
does not predict who will respond
to immunotherapy either.
Interesting that really is
unique, I think
for liver cancer, because I know in
other cancers we actually do look at
that and say, if we see
PD L1 expression then we know that
immunotherapy is going to be more effective.
So how do you decide who
to give immunotherapy to?
And who to treat with a TKI or a chemotherapy?
Yeah, that’s
a great question, and
until very recently the treatment has been a TKI first and then immune therapy, but I want to tell you about one of the newest combinations that’s been looked at, which is a combination of an immune therapy drug called atezolizumab. So that’s what we call a PDL1 antibody and it targets the immune system and then it was given in combination with bevacizumab which is an antibody against veg F which I had just mentioned before and that combination we had participated at Yale in the phase one study looking at this and I will tell you that out of the patients that I had on that study, I actually have two patients who had a complete response to treatment which was amazing to me, and they’re both still doing very well with no disease that could be seen on their MRIs which is something that I had never had happen before, so that was really exciting and the phase one study was positive and based on those results there was a large phase three study so they compared this combination back to sorafenib, which had been often given, as a first treatment and
they showed that there was a benefit of giving this combination immunotherapy and so that just got approved by the FDA a couple of months ago. And for patients who are good candidates for that which some people may not be a good candidate for getting that treatment, either because of the immune therapy part or the bevacizumab part, that’s become the new standard of care to give this combination. We see higher response rates. We see patients have longer responses to treatment. We don’t have a biomarker to predict who is going to do the best with that combination, but this is really a big change in our practice, just in the last few months to think about giving this type of combination to patients before starting with the tyrosine kinase inhibitor. So you know, we think carefully about each patient, and certainly there’s other immune therapy drugs to give and there are tyrosine kinase inhibitors to give, but the discussion now about how to sequence these treatments has become much more relevant. There’s other
studies looking at combination therapies that the full data has not been presented yet. It hasn’t been published yet, but there’s other studies that are showing more positive data than just giving a tyrosine kinase inhibitor by itself, and so it’s just been really exciting.

Stacy Stein is an associate professor of internal medicine in medical oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut public radio.