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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 that the same concept of fatty liver that we sometimes hear about? 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 HEP As 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 really 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
0:06:04.968 –> 0:06:06.716 through primary care,
0:06:06.72 –> 0:06:09.336 and especially through the VA system.
0:06:09.34 –> 0:06:10.238 Unfortunately,
0:06:10.238 –> 0:06:12.932 there’s a large burden of hepatitis
0:06:12.932 –> 0:06:16.309 C to really make sure that everyone
0:06:16.31 –> 0:06:19.355 is screened at least once,
0:06:19.36 –> 0:06:21.976 because we do have treatment now,
0:06:21.98 –> 0:06:24.59 which is important to know
0:06:24.59 –> 0:06:27.206 and make sure that’s started in
0:06:27.21 –> 0:06:31.125 a timely fashion.
0:06:31.13 –> 0:06:33.31 And screening is a routine blood test,
0:06:36.561 –> 0:06:39.692 so if you haven’t had a blood test
0:06:39.692 –> 0:06:42.908 and are in that baby Boomer generation,
0:06:42.91 –> 0:06:46.39 or you have been born in another country,
0:06:46.39 –> 0:06:47.95 it’s a good idea
0:06:47.95 –> 0:06:50.73 to at least get checked and
0:06:50.73 –> 0:06:53.514 see if you have one of these two
0:06:53.514 –> 0:06:56.649 hepatitides which may put you at
0:06:56.649 –> 0:06:58.805 risk of developing liver cancer.
0:06:58.805 –> 0:07:01.29 So let’s talk a little bit about
0:07:01.29 –> 0:07:03.855 that next step when you
0:07:03.855 –> 0:07:06.159 were talking about how if your
0:07:06.159 –> 0:07:08.409 liver enzymes are elevated that
0:07:08.409 –> 0:07:11.044 should really spur people on to
0:07:11.044 –> 0:07:13.546 thinking about liver cancer as a
0:07:13.546 –> 0:07:16.09 potential cause for that, so
0:07:16.09 –> 0:07:18.833 aside from an abnormal blood test of
0:07:18.833 –> 0:07:20.798 your liver enzymes being elevated,
0:07:20.8 –> 0:07:23.278 are there other symptoms that people
0:07:23.28 –> 0:07:25.296 should be looking for in terms
0:07:25.296 –> 0:07:28.107 of liver cancer or can it be
0:07:28.107 → 0:07:29.039 completely asymptomatic?
0:07:29.81 → 0:07:32.108 That’s a good question.
0:07:32.11 → 0:07:34.798 So what’s so interesting about liver cancer
0:07:34.8 → 0:07:37.327 is that it’s so tied to Cirrhosis
0:07:37.327 → 0:07:39.02 and underlying liver disease,
0:07:39.02 → 0:07:41.222 and so those two things obviously
0:07:41.222 → 0:07:43.629 are separate but also very related.
0:07:43.63 → 0:07:46.214 So you know the symptoms of the cancer
0:07:46.214 → 0:07:48.619 may not be traditional symptoms.
0:07:48.62 → 0:07:50.056 People think about,
0:07:50.056 → 0:07:53.32 we don’t have a lot of nerve endings
0:07:53.32 → 0:07:54.616 inside the liver.
0:07:54.616 → 0:07:57.053 So often people don’t feel a difference
0:07:57.053 → 0:07:59.615 necessarily the way someone might feel
0:07:59.615 → 0:08:02.2 a mass somewhere else in their body.
0:08:02.2 → 0:08:04.594 And unless there’s really tumor
0:08:04.594 → 0:08:07.181 pressing on the capsule of the liver
0:08:07.181 → 0:08:09.97 where there are a lot of nerve endings,
0:08:09.97 → 0:08:12.19 they probably won’t feel any different.
0:08:12.832 → 0:08:15.4 So a lot of the screening really winds
0:08:15.467 → 0:08:17.711 up being identifying the people at
0:08:17.711 → 0:08:20.08 risk of for Cirrhosis and identifying
0:08:20.08 → 0:08:22.486 cirrhosis and then looking at that
0:08:22.486 → 0:08:24.463 group and screening them with
0:08:24.463 → 0:08:26.418 imaging for liver cancer.
0:08:26.42 → 0:08:29.204 Because we know that the cure rate and
0:08:29.204 → 0:08:32.637 the success at treatment is better
0:08:32.64 → 0:08:34.968 the earlier we can find it.
0:08:36.062 → 0:08:37.882 So for patients that present with
0:08:37.882 → 0:08:40.329 a single liver lesion and they
0:08:40.329 → 0:08:41.973 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. Tell us a little bit about the imaging that needs to happen. 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
0:10:02.404 –> 0:10:05.365 expect in order to try to find a liver
cancer early, right?

0:10:05.37 –> 0:10:06.342 So there’s a few ways to image the liver,

0:10:06.342 –> 0:10:09.319 so sometimes for screening they
start with just an ultrasound,

0:10:09.32 –> 0:10:10.965 which is pretty easy to get, noninvasive.

0:10:10.965 –> 0:10:12.61 There’s a probe that is
put over the abdomen and is kind of pushed down,

0:10:12.61 –> 0:10:14.92 images that show up,

0:10:14.92 –> 0:10:16.248 and then there’s
images that show up,

0:10:16.248 –> 0:10:18.188 images that show up,

0:10:18.19 –> 0:10:19.188 and they could often find changes
of Cirrhosis and possible tumor.

0:10:19.19 –> 0:10:20.84 And when we’re really
concerned that there is cancer,

0:10:20.84 –> 0:10:22.064 the best imaging, what’s considered
images that show up,

0:10:22.064 –> 0:10:23.9 and they could often find changes
of Cirrhosis and possible tumor.

0:10:23.957 –> 0:10:25.767 And when we’re really
concerned that there is cancer,

0:10:25.77 –> 0:10:27.666 the best imaging, what’s considered
of Cirrhosis and possible tumor.

0:10:27.666 –> 0:10:29.39 for patients that are not able to
concerned that there is cancer,

0:10:29.39 –> 0:10:32.26 and we best want to characterize it,
concerned that there is cancer,

0:10:32.26 –> 0:10:34.696 the gold standard is really an MRI
concerned that there is cancer,

0:10:34.696 –> 0:10:37.415 for patients that are not able to
the gold standard is really an MRI

0:10:37.415 –> 0:10:39.795 get an MRI for one reason or another,
the gold standard is really an MRI

0:10:39.876 –> 0:10:42.556 we’re able to do a CAT scan with
for patients that are not able to

0:10:42.56 –> 0:10:45.104 something called triphasic imaging,
we’re able to do a CAT scan with

0:10:45.104 –> 0:10:46.98 where we’re able to get a very
good look at the liver also so

0:10:46.98 –> 0:10:49.213 most patients once there’s
where we’re able to get a very

0:10:49.213 –> 0:10:52.17 any real concern,
most patients once there’s

0:10:52.17 –> 0:10:54.095 they usually getting an MRI,
most patients once there’s

0:10:54.178 –> 0:10:55.81 and if not
they usually getting an MRI,

0:10:55.12 –> 0:11:00.23 a CAT scan and so
they usually getting an MRI,

0:11:00.23 –> 0:11:02.46 what’s the next step?
a CAT scan and so

0:11:02.46 –> 0:11:04.064 A biopsy now?
what’s the next step?

0:11:04.064 –> 0:11:06.079 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 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 is this primary cancer. Is this a secondary cancer? And hopefully get a little bit more in terms of clues that can help you to treat it. Absolutely and also what’s interesting is that 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. With liver cancer sometimes it’s what’s called Multi focal disease, meaning that it’s not really one area that spread to other areas. But that because of the cirrhosis you could think of the whole liver as being at risk for developing tumor, and so sometimes there’s actually more than one area at the same time that has developed a tumor. 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.

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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 multifocal. 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 couldn’t present 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 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 of these 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. So it’s more targeted therapy.

While sorafenib had some benefit, we all recognize that it wasn’t enough. And then if patients didn’t really tolerate it, than 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 I have a drug that can target. Yeah, that’s a really good question and there’s a few things that you asked 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 and 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.

Doctor 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.