

Support for Yale Cancer Answers comes from AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com. Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. 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 is a conversation about liver cancer with Dr. Mario Strazzabosco. Dr. Strazzabosco is a Professor of Oncology and Gastroenterology at Yale School of Medicine. Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore It is great to have you back on the show. I felt like we did an interview with you just a few weeks ago, but it turns out it has been over a year.

Strazzabosco Yes, indeed.

Gore First thing I would like to talk about and I think we probably touched base on before about this, is just to clear up for our listeners, you often hear "oh! My mother had breast cancer but then she died of liver cancer" or "My father had colon cancer, but he died of liver cancer." And that is not really correct for the most part, is that right?

Strazzabosco Well, we are talking here about primary liver cancer. You are referring to examples of what is called metastatic liver cancer or secondary liver cancer. In this case, the liver is actually pretty healthy.

Gore So it is really not liver cancer, it is really the other cancer which has spread?

Strazzabosco Yes, metastatic spread, and the liver is filtering all the venous blood from other places.

Gore So it is easy for the cancer cells to settle there?

Strazzabosco Right.

Gore But that is not what you study, right?

Strazzabosco No. What we study and treat is actually primary liver cancer. So, a cancer that originates in the liver.

Gore I see. What kind of patient gets that?

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Strazzabosco There are 2 kinds of cancer that originates in the liver, one more frequent than the other. The less frequent is called cholangiocarcinoma and that is a cancer that can happen in any patient. There are a few risk factors, but it is rare. The other which keeps us quite busy is the so-called hepatocellular carcinoma, also called hepatoma or HCC. This is a cancer that actually has

several risk factors. The most frequent one is chronic liver disease. So, it is a cancer that we find in patients that have some sort of advanced liver disease. Most of the time, these patients have viral hepatitis, hepatitis B, hepatitis C or they have a history of drinking alcohol or they have some genetic diseases of the liver that brings chronic liver disease, such as cirrhosis, and this is something which is becoming epidemiologically more and more important – they are obese, or they are diabetic. Most of the time, it is important to recognize that there are a combination of factors. It is not only one factor. The patient may be infected by hepatitis B or C virus, but in addition to that, he does not know it and so he lives a regular life, including during the weekend and is smoking and obese and overweight.

Gore Sounds like most of America, right?

Strazzabosco One thing that Americans do, which is good, we drink a lot of coffee and coffee apparently is good for the liver.

Gore Well, then I am in good shape and I do not smoke. Aren't viral hepatitis diseases treatable nowadays?

Strazzabosco Yeah. One important message that I would like to deliver is that most liver diseases are preventable and treatable. Specifically, your question is about viral hepatitis, and yes there are two major viruses that can cause chronic liver disease, one is hepatitis virus B and this can be suppressed. We have effective pills that can keep the virus at bay.

Gore But does not cure it?

Strazzabosco The virus is there. It cures the disease. The patient gets a dramatic improvement actually under this treatment. It does not really reduce the risk of cancer if you treat the patient when he is already cirrhotic. If you treat the patient before cirrhosis, the risk of cancer is reduced. But hepatitis B is an oncogenic virus, it integrates into the genome.

Gore You mean it causes cancer, per se.5:28 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0812-Podcast-Strazzabosco_340230_5_v1.mp3

Strazzabosco Yeah, it causes cancer per se. And so, there are populations in which you can get the virus very early in life, in which you can actually have liver cancer in the absence of relevant liver disease.

Gore And what about hepatitis C?

Strazzabosco Hepatitis C, it is causing liver cancer through another mechanism, mostly inflammation, regeneration and the liver tries to repair, and there are several mutations that accumulate slowly inside. So, hepatitis C now is curable. There are very effective drugs that can be administered to the patient, as a short-term treatment now.

Gore I see a lot of commercials where the people look very happy and they are sending balloons in the sky. That is good right?

Strazzabosco It is extremely effective and also collateral effects are really negligible.

Gore You mean, side effects?

Strazzabosco Yeah, the side effects. I remember the times in which we were giving interferon.

Gore Terrible, so terrible.

Strazzabosco It was a terrible drug and initially cured 20% of patients.

Gore And they felt like they had the flu all the time.

Strazzabosco Exactly. And then, slowly, slowly, slowly, this drug is clearly a magic treatment revolution. However, there are some disappointments. The fact that the risk of developing liver cancer if you are treated when you are cirrhotic is not zero, it's decreased, but still present and sizable. We see many hepatocellular carcinomas in patients that had been successfully treated with these new drugs. That does not mean that the drug favors the cancer, but simply that either the treatment was too late or that we are simply taking care of one of the risk factors. Most of the time, these patients are also diabetics or they may be obese or they may be drinking, and we fool ourselves into thinking, okay the virus is gone, the patient will not have cancer, whereas we need to realize that we need to treat the patient in entirety, the whole spectrum of risk factors need to be addressed by the treating physician. We need them to have a good control of diabetes, we need to reduce their metabolic syndrome risk factors, which are the same as cardiac disease interestingly.

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Gore What does cirrhosis mean?

Strazzabosco Cirrhosis means that the liver, after a long fight against an offending agent, tries to contain it, but by doing that shows the scar of the battle, and so the liver rather than remaining a sponge which is easily perfused, it becomes like a more rocky fibrous tissue in which the perfusion is as effective, but also needs to have higher venous pressure, and so cirrhosis is usually a combination of cell death, cell regeneration and fibrosis.

Gore Now, does everyone who has cirrhosis know that they have cirrhosis?

Strazzabosco Unfortunately not. Cirrhosis may remain clinically silent for many, many years. In fact, we hepatologists distinguish it as compensated liver cirrhosis and decompensated liver cirrhosis. The compensated – some of the complications they are ascites, yellow discoloration of the skin, encephalopathy, confusion, kidney failure.

Gore These are really sick people.

Strazzabosco Yes and hematemesis, vomiting blood. These are very sick people that need immediate transplantation if possible. But most of the interest now is actually in what to do before that stage. Because when you reach that stage, again you either have a liver transplant or we can do a lot for you, but your survival is limited.

Gore I see. I know many good primary care physicians are screening, especially the baby boomers seem to be at high risk for hepatitis C, you don't have to tell me why, but you know there are people being screened and if it is found, I guess they are getting treated, but how would they know if they have cirrhosis or not? Do the doctors screen for that?

Strazzabosco Not really. You have several conditions in which you may present to your primary care physician. One is you are baby boomer, so you lived through the 60's.

Gore You might have ingested things.

Strazzabosco Yeah, you may have been involved in several of the promiscuous risk factors of the 60's and so on.

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Gore That didn't happen in Italy?

Strazzabosco No. And of course, in the US, the guidelines are actually to screen for hepatitis virus in this population of patients. If you turn out to be positive, surely your doctor will at least run certain liver labs and ultrasound. While done with ultrasound, they will give you information on whether or not your liver is already cirrhotic or not. You can then be referred to a hepatology center and they will use elastography.

Gore Elastography! What is that?

Strazzabosco Elastography is a machine that looks like an ultrasound that is to give a flick on your liver and measure how hard it is.

Gore Well, that sounds like it hurts.

Strazzabosco No, it does not hurt, but one thing is knocking on a mattress and one thing is knocking on the wood, you hear different sounds.

Gore Got it.

Strazzabosco So, this little machine basically records the elastic wavelength, and if your elasticity is not enough, your resistance, you are in either the cirrhotic or pre-cirrhotic phase.

Gore We are going to have to talk about that in a minute, because I do not want you banging on my liver, but right now, and I do not want you to ask me what I was doing in the 60s either, we are going to take a short break for

a medical minute. Please stay tuned to learn more about liver cancer with Dr. Mario Strazzabosco.

MedicalMinute Support for Yale Cancer Answers comes from AstraZeneca, a leader in oncology research with 4 new FDA-approved medicines in the last 3 years. Learn more at astrazeneca-us.com. This is a medical minute about colorectal cancer. When detected early, colorectal cancer is easily treated and highly curable. And as a result, it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Tumor gene analysis has helped improve management of colorectal cancer by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in more patient-specific treatments. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest Dr. Mario Strazzabosco and we are discussing the surveillance and treatment of liver cancer. Mario, before the break, you were telling me that in patients who are found to have hepatitis virus, though usually even ultrasound and this scan which measures the firmness or texture of the liver, if somebody has a positive result on this ultrasound test, then what happens?

Strazzabosco So, if a patient has positive results in the FibroScan or diagnosed with suspicious advanced liver disease or cirrhosis, the important thing is to understand that he has to undergo so-called surveillance for hepatocellular carcinoma. So, every patient with cirrhosis has a risk of developing hepatocellular carcinoma. 5% of our patients with cirrhosis will show up every year with liver cancer.

Gore 5% per year?

Strazzabosco Yeah. And after 10 years, there is a good size of patients. And we have a lot of possible approaches to cancer that are small.

Gore Small cancers?

Strazzabosco Yeah, by small we mean less than 5 cm in size.

Gore Okay that is pretty big.

Strazzabosco And better if they are less than 2. So, how do we pick them up? By doing an ultrasound every 6 months. Because 6 months is more or less the doubling size of the tumor. So, the guidelines internationally, they recommend 6-month ultrasound. Now, there are differences in the way the ultrasounds are done through the world and so on and so forth. So, there are some countries that use an Alpha-fetoprotein (AFP) test.

Gore This is a blood test?

Strazzabosco Yes. That is a biomarker of possible hepatocellular carcinoma. The problem is not everybody is positive for that, actually a minority of patients.

Gore Not all the patients with liver cancer have that?

Strazzabosco Right, actually less than 50% and you need to monitor the growth of the biomarker during the time. So, basically, ultrasound every 6 months plus an alpha-fetoprotein determination. That has been shown to be effective. There are data that show, or meta-analysis that show, that the patients that are undergoing diligent surveillance

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will have increase of viral and increased chances to have the tumor diagnosed at an early phase.

Gore And what happens then if the tumor is diagnosed early?

Strazzabosco Right. What happens is that, we have a lot of things to offer. Our usual way we go through it during the tumor board is if the patient can be resected, surgical resection, and not all of them can because there is portal hypertension, there is treatment criteria that are associated with good survival after resection or with dismal prognosis because of decompensation. The patients that cannot be resected, then you start considering whether or not they are transplant candidates.

Gore For liver transplants?

Strazzabosco Yes, because hepatoma is the only solid tumor that can be transplanted, but up to a certain stage. So, we can transplant patients. I do not want to go into detail, but the message is, early cancer can be transplanted. And then, we need to understand how long the waiting time is.

Gore Finding the right organ?

Strazzabosco We will do what we can in order to keep the tumor at bay while we wait. And this is mostly achieved through an interventional radiology approach. Interventional radiology has been a major factor in the improvement in their prognosis.

Gore So, what do they do?

Strazzabosco There are several ways in which they can address the tumor. If the tumor is still relatively small, they can use ablation technologies. So, they insert a probe and then use some radiofrequency wavelength to cook it.

Gore They are zapping it.

Strazzabosco Yeah. Or they use cryoablation.

Gore Cold, that is freezing it.

Strazzabosco Exactly.

Gore You can cook it, you can freeze it.

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Strazzabosco And you can use microwave.

Gore That is disgusting.

Strazzabosco Yeah, it is truly disgusting.

Gore I will never eat in the microwave again.

Strazzabosco But it is actually extremely effective. And it is not a possibility if the tumor is too big, or based on the location of the tumor, if it is close to certain vessels or certain other organs. Then, they can use intra-arterial approaches. So, they will go through arteriography. They will reach the hepatic artery and go as much as possible, close to the feeding artery of the tumor because the interesting thing is this tumor is highly vascularized, and on the contrary to the normal liver which has a venous vascularization, they actually have an arterial vascularization. So, that can be embolized blocking the feeding of the tumor and also treated with high concentration chemotherapeutic agents or you can add some beads that contain radioactive compound, Yttrium-90 and so you sort of concentrate radioactivity in the tumor. So, these are effective approaches. The problem is that they do not cure the cirrhosis, and this cancer unfortunately comes back. 60-70% of the patients experience a recurrence in the 18 months following the first treatment. So, what we do actually now in our center, we follow them every 3 months with imaging and we go back again and again, and every time, it is like the first time, we go through their whole possibility of treatment, we see what we can do and by doing that, which is called a multi-modal approach and tailoring of the treatment and repeating the treatment several times, we go on until we can transfer the patient or if the patient is not a transplant candidate, until the liver function can sustain the treatment. More recently, there are targeted molecular approaches that are being used.

Gore Drugs?

Strazzabosco Drugs like TKA inhibitors that block intracellular signaling molecules that are important for that. At least 3 of them are now on the market and now also of course everybody is very interested in understanding what the role will be of immunotherapy. Recent trials show the possibility of adding immunotherapy after the patient has been treated with TKA inhibitors. So, it is a scenario which is

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changing dramatically and maybe in the future, we will try to expand the indication for medical treatment rather than using interventional approaches until the end. So, it is a changing world but it is too early to predict.

Gore And in the patients who successfully have a transplant, what are the chances of the cancer coming back?

Strazzabosco There is unfortunately the chance of the cancer coming back after a transplant even 2 years after the transplant, and that is a fascinating biological question, but the protocols that we use to identify the patient that can be transplanted is based on staging, but let us say that minimizes the chance of recurrence, so less than 10% of them will experience a recurrence if you use stringent criteria.

Gore Meaning the people who have earlier, smaller disease, right?

Strazzabosco Yes. And there is of course the tendency to expand the pool because you have to have a predicted survival of 70% at 5 years, but 65% survival with malignant disease is fantastic, right. So, there are at times expanding of this criteria, but a colleague of mine says it's like a Metro ticket. The faster you go, the more you pay, and so being a liver graft is a very rare commodity.

Gore Sure, there are not too many livers around.

Strazzabosco Exactly. So, it is imperative to wait, to weigh what is the best indication between oncologic indication or other indications, that is always the tension and the discussion, but I say we do a pretty good job with several iterations.

Gore So, if somebody is found to have earlier stage liver disease and they stop their risk factors, let us say they have hepatitis C treated and they have stopped smoking and if there is alcohol, maybe they stop drinking, can the liver fix itself at that stage?

Strazzabosco We used to think that cirrhosis is irreversible, what we learned with treatment of hepatitis B and C is that that is not completely the case, but there is a point in which the cirrhosis does not reverse. It is easier to identify this point clinically. For example, we published a paper showing that if you use the new antiviral and MELD score, MELD is a way we give a number to how sick the liver patient is. If the MELD score is around 20, which is in the middle, the patient can clinically revert, not pathologically get much better but clinically get much better. Above that, he will still need to be transplanted. The same is true for alcoholic liver disease where we have this 6 month rule, so the patient needs to wait 6 months before being

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transplanted and one of the reasons is first of all you have to make sure he is not going to go back to drinking, but the other reason is that it may improve itself. Gore And then you do have to do the transplant?

Strazzabosco But the people that do not improve by 3-4 months, they will have cirrhosis which is shrinking the liver and there is no way you can regenerate from there. That is, you cannot come back from that point.

Gore So, there is a possibility to revert.

Strazzabosco And certainly, if you do have liver cancer, make sure you address all your risk factors because that helps us, because in order to provide you with as many treatments as possible, you have to have good liver function. Also, for the new medical treatments and new agents, the studies are made always in patients with very well-conserved liver function and tolerability is better. So treat your liver very well.

Dr. Mario Strazzabosco is a Professor of Oncology and Gastroenterology at 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. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.