

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Dr. Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center, Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about liver cancer with Dr. Tamar Taddei. Dr. Taddei is an Associate Professor of Medicine and Digestive Diseases at Yale School of Medicine. Here is Steven Gore.

Gore Digestive diseases, is that gastroenterology?

Taddei Yes, it is. And gastroenterology is a very big field and we cover the entire digestive tract. In gastroenterology as a field, you may find many subspecialties, my subspeciality is the liver.

Gore The liver, which is hepatology is that right?

Taddei Correct.

Gore And the liver is an important organ, right?

Taddei It is the power house of the body.

Gore What does it do?

Taddei It does a lot of things silently that you cannot exist without. It actually is responsible for metabolizing many of the drugs that we take, many of the foods that we eat, and it is responsible for making clotting factors so without a liver you would bleed to death. It is responsible for all metabolism of cholesterol and other major pathways upon which the human body is dependent. I think that the biggest risk of liver failure is obviously we worry about bleeding to death but you would see a person who does not have a functioning liver being very jaundiced. The liver handles all the bile, which is delivered to the digestive system to digest food. I cannot tell you how fantastic this organ is and most people grow up their whole lives and do not even know where it

is. It is the second biggest organ in the human body apart from the skin and it is nestled right under a right rib cage.

Gore Under the rib cage, I thought that is where the lung is.

Taddei Right, so the lung takes up the majority of the rib cage but as you get towards those lower two ribs that is where your liver is, sort of tucked in right there underneath your lung.

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Gore Is that what my doctor is feeling for when he is digging his hands so deeply and I have to take a deep breath?

Taddei Correct, and oftentimes I even tap a little bit on your side and that is a way that the doctor can get a feel for how big your liver is.

Gore How do I know if I have a liver problem?

Taddei Sadly and very importantly you will not know until it is too late. Many people do not present to the doctor until they have very advanced liver disease and the reason is that you actually do not feel sick until your liver is functioning somewhere under 30% and in many cases even under 10%. We have a lot of reserves, the liver is a very forgiving organ, but if you have a lot of scarring in the liver then the organ can't regenerate. The liver is really the only regenerating organ in the body and in fact, if you have exposures that predispose you to developing scarring in the liver, then that can actually prevent your liver from recovery and what we call cirrhosis is the end stage of that scarring effect.

Gore Well I do not drink very heavily so I am not at risk for any liver disease, right?

Taddei No, it is true that we associate alcohol with liver disease, but a lot of that really depends on our genetic makeup and how much alcohol we consume. For example, you can meet people who might consume quite a bit of alcohol and never develop cirrhosis and people who consume very little alcohol

but regularly do develop cirrhosis and that is why there are guidelines about how much alcohol we should be drinking. An average male should drink no more than two alcoholic beverages a day and an alcoholic beverage is 4 ounces of wine, 12 ounces of beer or 1 ounce of spirits and for a female it should be no more than one drink a day, and to be honest with you, the pattern of American drinking is one that is very much binge drinking, you know we say weekend warrior or that kind of thing and the truth is that kind of drinking is especially toxic to the liver.

Gore Really?

Taddei Yes.

Gore But are there other things which can cause liver damage outside of alcohol?

Taddei There are many other things and actually a lot of people develop liver disease for totally other reasons. There are many genetic liver diseases, there are diseases of iron storage, copper storage and things that can be hereditary, but I would say that what we see most of is viral hepatitis, especially hepatitis C and in some parts of the country hepatitis B, and probably the biggest sort of new wave of liver disease if you will is the epidemic of obesity. It is bringing with it a syndrome called non-alcoholic steatohepatitis. It is a form of hepatitis caused by excess fat in the liver.

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Gore Well we want to talk about that some more later on. How would I know that I have had liver disease if I am not in this end stage with cirrhosis, how would I find out about that?

Taddei There are routine tests, so if you go for a physical, your doctor will often look at certain blood counts as well as a physical exam and on physical exam the doctor will examine your abdomen and look for whether your liver is small or whether your liver is large, whether they can palpate a spleen because in many people with end-stage liver disease they actually develop a large spleen and we look for findings on the scan and various things to see if there are any suitable, what we called surrogate markers, of liver disease. The lab work is often very helpful because if we do see as a person developing cirrhosis, there

is a drop in the platelet count and oftentimes a drop in the serum albumin, which is a measure of protein that the liver makes and we are really trying very hard to educate primary clinicians on what to look for to diagnose these things as early as possible, but liver disease is often not thought of until it is quite late. Now the CDC came out with a guideline in 2012 that actually calls for all baby boomers born between 1945 and 1965 to have one time hepatitis C testing. No matter whether you think you have risk factors for hepatitis C or not because three out of every four people in the United States with hepatitis C was born in that generation and by doing this, we think we probably have identified at least a million more people with hepatitis C and now that we have drugs that can cure hepatitis C, I would urge everybody to go out if you were born in that timeframe to be tested. Certainly, people who engage in IV drug use, even once in your life, even if you just tried it, and also with intranasal cocaine, even if you just tried it, it is possible that you could have contracted hepatitis C. People who have gotten tattoos perhaps in a parlor that did not use sterile ink pots or sterile needles could have contracted hepatitis C and certainly people who are exposed to blood either in their profession or if you are a medic that kind of thing, you should get tested.

Gore Is there sexual transmission as well?

Taddei It is extremely rare for hepatitis C and much more important with hepatitis B. The sexual transmission rate for hepatitis C is probably less than 3%. Certainly, there are riskier behaviors that may make it more likely, but it is very uncommon.

Gore Let's say, I am a baby boomer born in 1957, and let us say that I went to my internist and am tested for hepatitis C and he found that I had it, but I am feeling great, why should I be treated?

Taddei Hepatitis C is a different virus in different people. Of 100 people infected with hepatitis C, 25 of them will go on to develop cirrhosis within the next 20 years.

Gore 25%?

Taddei Yes.

Gore That is huge.

8:47 into mp3 file <http://yalecancercenter.org/podcasts/2014%201005%20YCC%20Answers%20-%20Dr%20Taddei.mp3> Taddei It is huge. And actually if you think about hepatitis C in sort of the natural scheme of medicine, it is a pretty new disease. We did not actually identify the disease until the 80s and we did not have an assay to actually test for it until the 90s. So we are not entirely sure of the natural history of the disease, so when we say 25% will have cirrhosis in 20 years, I am not really sure if a higher percentage might have cirrhosis in 40 years. So it is important to get tested and it is important now to think about being treated. Most people, as I said, will not have any symptoms at all until their liver is extremely sick and that is the impetus to get treated and in the past people were extremely afraid of treatment because it was usually a one year commitment with injectables every week and and that was usually interferon and many people feel horrible and so many people who have actually tried to treat their hepatitis C in the past have such horrible memories of that and really the response rate was one of chance, 50%, and they are stuck in this, I never want to hear about it again, but now we are able to offer oral therapies so no injectables, a very short course, 12 weeks with nearly 100% cure, so now is the time.

Gore Wow! That is really exciting. I thought we were still doing interferon and I do not want to take that if I do not have to.

Taddei Right, now you do not.

Gore That is incredible. So the message to my co-boomers out there should be go get yourself tested if you have not been.

Taddei Absolutely.

Gore And they can do that at their internists at their regular yearly physical exam?

Taddei Correct.

Gore So outside of liver failure and all the problems that I was taught that we associate with cirrhosis, is there an association between these problems and liver cancer, I know you work interactively with the GI cancer people.

Taddei Correct, my role at Yale is really running the liver tumor board and trying to deliver as comprehensive care as possible to liver cancer patients and many times these patients are different than other cancer patients because this cancer pretty much uniformly arises in a sick organ. About 80% of the patients diagnosed in the United States have underlying cirrhosis and obviously as a cancer grows in the liver, if the liver is already scarred, then clearly that liver is at even higher risk of developing failure because the cancer outstrips whatever functioning liver that person has. So I actually manage these patients in Smilow with a GI oncologist because there are drugs that we can offer, but the issue is, this needs to be co-managed and there are many disciplines involved because there are many different types of treatments for liver cancer. It is a cancer that is very much outside the oncologic box, if you will. The issue with liver cancer is that treatments are

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unusual because for more than 30 years it was considered to be chemotherapy and radiation resistant, and there are many, many studies of all kinds of chemotherapeutic regimens that were tried and had very little hope of any kind of cure or prolonging life, and it is a highly lethal cancer and in that vacuum grew the specialty of interventional radiology. A lot of the treatment that we offer a liver cancer patient is what we called local regional therapy or direct therapy right into the liver. We can burn the tumors. We can freeze them. We can deliver chemotherapy into the tumor and then choke off the tumor's blood supply. I know it sounds out there, but sometimes when you have a vacuum, other things will come to the foreground and in the beginning stages of liver cancer oftentimes your go to people are either surgeons, if you have preserved liver function and can undergo a liver resection. Surgeons if you have underlying liver disease that would not allow you to undergo resection, but you have tumor that will allow you to be transplanted and that we can talk about a little bit later, but liver transplant is really an amazing thing that can offer a durable cure to a patient with liver cancer and then after that we go to the interventional radiologist who can often keep tumor at bay while the patient waits for transplant or certainly prolonged life considerably and then once we move into more palliative therapies, interventional radiology still has a role and then we can think of systemic therapies like sorafenib, which is an FDA approved drug for liver cancer.

Gore We are going to go to break in a minute, and you have me a little freaked out about the whole idea of burning my liver. Maybe we can take that up after the break and some of the other interesting things that you have

mentioned. We are definitely going to want to follow up. Right now we are going to take a short break for medical minute.

Medical

Minute In 2014, 200,000 Americans will be diagnosed with lung cancer and in Connecticut alone there will be over 2500 new cases. More than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. New treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for lung cancer. Advances are being made by utilizing targeted therapies and immunotherapies. The BATTLE-2 trial at Yale aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non-small-cell lung cancer. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut's public media source for news and ideas.

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Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my guest Dr. Tamar Taddei and we are discussing liver cancer. Tamar, before the break I joked that it was scary to hear about burning and freezing the liver. I am sure I am not the only one, so can you tell me what that is about.

Taddei So thermal or toxic techniques can kill tissue and it can kill cells that you do not want. Think about it like a wart. When you go and have your wart frozen by the dermatologist, you are killing the wart cells by freezing them. So, what we can do in the liver, is a similar technique, we actually put a probe into the liver, you can do it through the skin or if it is a very difficult part of the liver to reach, you can do it laparoscopically, and you put a probe into the center of the tumor and you actually burn the tumor. So you can burn them, you can microwave them, you can freeze them.

Gore Wow!

Taddei Yeah there are all kinds of techniques, and those techniques are called ablative therapy.

Gore Is it painful are people asleep, how does that work?

Taddei People are under conscious sedation. So they are sort of able to follow commands, but they really do not remember anything after the procedure and it takes about an hour or two and they leave the hospital the same day and they may have pain, certainly any time you kill tissue you can have pain, but usually it lasts a matter of a couple days and then they go back to their daily routine.

Gore And that really helps shrink the cancer?

Taddei Yes, it is a very good directed therapy for liver cancer.

Gore Fascinating. Before the break, you also talked about liver transplant for cancer, which shocked me.

Taddei It is shocking and it is actually something that people really ought to be aware of, so liver cancer is actually the only solid organ malignancy for which transplant offers a cure. When we think about bone marrow transplant for blood cancers, it is sort of a similar thought, but what you do is you simply remove the liver and you put a new one in. That should freak you out more than burning a liver.

Gore Well, yeah.

Taddei Liver transplant really only became an indication for treatment in 1996, when a New England Journal paper came out with 48 patients that were catalogued, and a 48 patient paper to hit the New England Journal is actually pretty amazing, because usually those are papers that comprise thousands of patients, but the findings were absolutely remarkable, which were that if you remove the liver, when you have no more than three tumors, which are no more than 3 cm a piece, or one 17:46 into mp3 file <http://yalecancercenter.org/podcasts/2014%201005%20YCC%20Answers%20-%20Dr%20Taddei.mp3> tumor, no more than 5 cm, you can actually have an 85%, 5-year survival, which is an oncologic fantastic survival and also in the transplant world is an excellent survival. When you talk about prolonging life, it is very important to remember the different worlds that liver cancer lives

in. So in the transplant world, if you are going to get a liver transplant, your survival has to match the survival of everybody else who gets transplanted for liver disease, so for end-stage liver disease and that 85%, 5-year survival is really what you are looking for. That is very different than oncologic survival where if we can get a 50% 5-year survival we are very happy, but that would not pass muster at a transplant center and that is really why transplant is highly regulated for liver cancer. Now, the issue about liver cancer and transplant is that here we have these numbers right, three tumors no more than 3 cm, one tumor no more than 5 cm, but clinically not all these tumors follow these descriptive patterns. I have seen patients who have 10 cm tumors that have treatment for that tumor and they live 10 more years, and I have seen people who have a 1 cm tumor that 6 months later might have completely overtaken the liver. We do not know enough about liver biology to really know who benefits most from transplantation and so there is a lot of study going on to try to figure out, is there an optimal tumor burden, perhaps we could transplant more patients and give them many-many decades of survival and so this is an area of very hot debate in the transplant world and because you have two populations waiting, a population of patients who may have cirrhosis, but really have not developed jaundice and liver failure, but they have a tumor and a population who has developed liver failure and they desperately need that organ, and how do you make sure that you are benefiting equally those populations? That is very difficult.

Gore What about that new kind of transplant that I have heard about where they give you a piece of somebody's liver from a living donor. Is that applicable here?

Taddei Absolutely, and we do have a tremendous donor shortage especially in this region. This is the United Network for Organ Sharing Region 1, in this part of the country, which is basically everything North of New York up to Maine, it is very hard to get a transplant and for that reason we really urge patients to think about living donors and these are the people who are friends with the patient, they do not have to be a relative. There are a lot of misconceptions about living donor liver transplant. All you have to match is your blood group. It is not like it needs to be one of those 6/6 kidney matches that you always hear about. It is pretty amazing, if you have a good donor and a good recipient, it is really an elective surgery. Obviously I am biased by my observations at Yale because we have two of the best living donor surgeons in the country under one roof, so we are extremely privileged, but it is wonderful because you are not taking away from the cadaveric pool, so you are not taking livers from people who are dying of end-stage liver disease and you can plan it according to optimal time for surgery as well as the donor's optimal time.

Gore This is so fascinating and overwhelming to think about, but for the donor who is losing part of their liver, what is their recovery like and what is their life like after that?

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Taddei As I said earlier, the liver regenerates and so if you have no scar in your liver and these donors have to be healthy adults, under 55 years of age with no major medical problems, their liver will grow back in six weeks to fill the cavity from where half of their liver was removed and they go back to their life normally and it is pretty amazing. Yes, they have had a major surgery and they have a usual recovery from a major surgery, but it is amazing how quickly the liver regenerates and these people actually feel very well and there are studies going on to sort of figure out who is a living donor and what is their life like afterwards and actually many of these people have extremely positive experiences because of the altruism of allowing another person to stay alive.

Gore Yeah that is an amazing experience to help somebody stay alive. What is the quality of life for the patients who had liver transplant, whether it be a cadaveric transplant or one of these living donor transplants, assuming that they remain cancer free, I assume that they are taking anti-rejection drugs and so on?

Taddei Correct, and anti-rejection drugs have come a long way. Most people will need to be on one or two drugs for the rest of their life but, it is drugs that they take once or twice a day, they generally feel very well, I mean especially for the end-stage liver folks who were so sick for so long it is really a second chance and it is like a night and day transformation. But I think also psychologically knowing that you have gotten rid of your liver cancer, even if you weren't terribly sick leading up to the transplant, but it's always a game of roulette, every three months you are having an MRI, what if it grows, what if it comes back? So I think that psychological burden for the liver patient who is waiting for a transplant with a cancer is overwhelming really. So, the quality of life is excellent. Their healthcare after transplant is not that much different from routine health maintenance before transplant in the sense that they go to the doctor maybe once a year to get their cholesterol checked, etc. usually the first year after transplant you are seeing the doctor a lot but after that not so much and you are mostly getting routine testing, blood testing to just make sure that your rejection levels, the medicines that you are taking, we can actually measure the level in your blood, to make sure that you do not reject.

Gore And it used to be that with people on anti-rejection medicine there were a lot of infections, is that not the case anymore?

Taddei Not so much, we worry most in the first 3 to 6 months and during the first 3 months the patients are usually on quite a few medicines to prevent what we call opportunistic infections or infections in a person with a depressed immune system. But the liver is actually a very forgiving organ, for example, unlike the kidney, which cannot tolerate rejection at all, the liver actually can tolerate rejection and it is treated very easily and our goal as transplant hepatologists is to actually ride the immunosuppression as low as possible, so that they do not develop any kind of infection, but also just to make sure that the body can continue its immune surveillance function. One of the things that we survey on a daily basis is cancer cells, you and I may have a couple of circulating cancer cells, but our immune system is saying, 'hey, you are not right' and kicks it out. So when you

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transplant a person for liver cancer you really want to be sure that you are not suppressing their body's ability to continue that surveillance. There are certain immunosuppressants that may have a role in anti-cancer, so we do look at those more commonly in a person who has been transplanted for liver disease, but the idea in liver transplant is really to avoid over-immunosuppression.

Gore As big a deal as it sounds like it is, at the end of day some of these patients are being cured and have excellent quality of life.

Taddei Absolutely,

Gore That has got to be very gratifying for you, and a nice outcome for them.

Taddei Absolutely,

Gore While we still have some time, you kind of freaked me out a little bit about this epidemic of obesity and this complicated hepatitis C you

were telling me about, and I bet a few of our patients, like me, have not been as successful on their Weight Watchers plan as we wish we were.

Taddei Again as we talked about with alcohol, a lot of it really depends on your genetic makeup. As a society we are becoming obese. It is in the literature everywhere. Children are now obese, and in adults, at least a third of the population is obese. So, what happens in a person who has obesity and their genetic makeup is to have this risk factor of aberrant fat handling or bad fat handling, they develop fat in their liver that can really be toxic to the liver and can cause scarring. First it causes inflammation, then it causes scarring and that scarring can ultimately lead to cirrhosis. We are seeing liver cancer in patients with this type of hepatitis, this non-alcoholic steatohepatitis, and what is alarming is that it is now being described that we are seeing it before they develop cirrhosis. Now, the guidelines for screening for liver cancer really are only in patients with cirrhosis. So it sort of begs the question, how do we approach this population? If you are carrying around an extra few pounds, should you be nervous that you have this? Usually a routine blood test at your yearly physical will check liver tests. If they are not abnormal you should not really worry about it that much. If you have a family history of liver disease and you come from a family that has been heavy, if you have a family history of diabetes, these are sort of some of the more likely risk factors, so we see the syndrome mostly in people who have hypertension, high cholesterol, and diabetes, that is the most at risk group, but there are people who do not have diabetes and get fatty liver disease. There are certainly families that have a long line of obesity and liver disease that nobody has been able to diagnose. This syndrome, I think much of it used to be lumped into this term of cryptogenic cirrhosis, which basically means, we do not know. But now we are beginning to know and what is very interesting is by the time they come to me they have usually lost a lot of the weight because their liver disease is so severe that they cannot maintain their muscle mass and they lose the weight. So oftentimes I will say, could you bring me a picture of what you looked like before you became ill and sure enough they were considerably overweight. We worry about people who have centripetal obesity meaning that they kind of look more like an

28:22 into mp3 file <http://yalecancercenter.org/podcasts/2014%201005%20YCC%20Answers%20-%20Dr%20Taddei.mp3> apple than a pear, so a lot of their fat is what we call visceral fat or the fat that sits on your belly and we are actively trying to figure out how to treat these folks, but the mainstays of treatment really are exercise and weight loss and the problem is that we have a culture of lots of sugars, lots of carbohydrates and it is extremely difficult to tell a patient to lose weight and not actually give them the real tools to lose the weight. They need to meet with the nutritionist. They should be involved in a program that can educate them on how to exercise and lose weight. Yale is actually starting a program, a metabolic program, for folks who need to lose weight and ideally

we should see anybody who is obese but certainly those with liver disease or heart disease, we want to see as early as possible. Now what is really sad is that it used to be that we said, 'Oh, we are not going to worry about these people, because they are going to die of their coronary disease long before they die of the liver disease, but the truth is that cardiologists have gotten so good at medically managing obesity related heart disease that we are actually seeing these folks now in droves.

Dr. Tamar Taddei is Associate Professor of Medicine in Digestive Diseases at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber and hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.