

Dr. Sukru Emre and Dr. Mario Strazzabosco, Leading the way to Treat Liver Cancer December 6, 2009 Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed welcomes Dr. Sukru Emre and Dr. Mario Strazzabosco. Dr. Emre is a Professor of Transplantation and Chief of Transplant Surgery at Yale New Haven and Dr. Strazzabosco is a Professor of Internal Medicine focused on Hepatology.

Chu How many patients are diagnosed each year with this disease? Emre Liver cancer is a worldwide problem. Its estimated mortality annually is above 600,000 people worldwide. The incidence varies according to geographical areas and this is due to the different incidence of the risk factors, of course. So, if it is extremely high in Asia and some parts of Africa and some Mediterranean countries, it is less frequent in western countries like the USA; however, it is rising even here.

Chu Mario, give us a sense of how many patients are diagnosed with liver cancer in the United States? Strazzabosco In the United States we have a mortality rate of 7,000 people per year and a prevalence, which means the number of patients that are sick, of 18,000, and in Connecticut, from where we speak, statistics performed around five years ago show that there are at least 180 deaths per year due to liver cancer.

Chu It's a pretty significant disease? Strazzabosco It is indeed.

Chu Sukru, there is now this appreciation that the incidence of liver cancer, certainly here in the United States and I guess in some other western countries, is steadily increasing. I know some of the numbers that are projected out 10 to 15 years now are pretty staggering, why is that? Emre Well the increasing number of persons living with cirrhosis is likely the explanation for the increasing incidence of a hepatocellular carcinoma resulting from a combination of factors, including increasing incidence of cirrhosis caused by hepatitis C cirrhosis, to a lesser extent hepatitis B infection, and general improvement in survival among cirrhotic patients. It has been estimated that hepatitis C began to infect large numbers of young adults in North America and South and Central Europe in the 1960s and 1970s, as a result of intravenous drug use. So the virus then moved into National blood supplies and circulated until a screening test was developed in 1990. After which time, rates of new infection decreased dramatically. Currently, it is estimated that a CV related HCC will peak around the year 2010, next year. If I summarize, we are helping people survive hepatitis related cirrhosis, that might be hepatitis C, hepatitis B, alcoholic liver cirrhosis, or hemochromatosis, all these cirrhotoses, whatever the underlying etiology, sets the stage that the liver cells then can change their regular rhythm, and then they develop cancer. So, since we are surviving longer we are going to see more and more hepatocellular carcinoma. One more thing I would like to say here is that our estimate, after the diagnosis in cirrhosis in hepatitis C patients, within five years approximately 25% to

30% of patients will develop hepatocellular carcinoma. Chu Mario you had something to say? Strazzabosco Sukru raised two very important points. In our countries, this cancer rarely happens in patients without liver cirrhosis. It is mostly a consequence of chronic liver disease. And the second point that Sukru raised is that it takes a long time to go from hepatitis to cirrhosis, to cancer, and we estimate that this time can be between 20 and 30 years, and this is why we are seeing now the cohort of patients that were infected 20 years ago before we started to use the interferon and other antivirals, had the time to develop cirrhosis. This is why we project that in the next 10 years the incidence will raise even more. Chu Maybe we can just review for our listeners, what are the main causes for chronic liver disease, cirrhosis that you talk about, which then leads to liver cancer? Strazzabosco Every kind of cirrhosis may ultimately lead to liver cancer, although there are differences; some etiologies are more closely related. For example, the hepatitis B virus is a direct oncogenic virus that can integrate into the DNA and favor the expression of proto-oncogenes. Emre If I can add, in the United States and Europe the main reason is hepatitis C, and in Asia and the southeast part of the world, it is hepatitis B followed by hepatitis C, and other things such as chemicals like alcohol and aflatoxin. We do not see aflatoxin related hepatitis HCC in this country, and also we have hormones such as exogenous, steroidal sex hormones, and we have cirrhosis related to metabolic diseases, such as tyrosinemia, such as primary hemochromatosis, alpha 1 antitrypsin, and of course these diseases will be effected and there are other factors modulating this such as sex, such as age, and race that will be effecting the increasing or decreasing the number of hepatocellular carcinoma cases. 7:04 into mp3 file <http://www.yalecancercenter.org/podcast/dec0609-treat-liver-cancer.mp3> Chu For a long time it was felt that in this country, in the United States, that alcohol-related liver disease, cirrhosis, was a main reason for liver cancer, Mario your thoughts on that? Strazzabosco As we said, all possible causes of liver disease, if left untreated, will lead to cancer, but there is an important point to make here that most often patients that progress to cirrhosis and then to cancer have more than one risk factor, it is the association of different risk factor that increases dramatically the relative risk. So, if you have hepatitis C and you do not know it, and you drink socially and maybe you are overweight, your risk of having the cancer increases dramatically. If patients acquired the virus when they maybe were using IV drugs when they were younger and they have a co-infection, hepatitis B and C, even if the hepatitis B has been longly nonactive, the risk of infection increases dramatically. And now we have another player coming into the game that surprises all of us, which is fatty liver and steatosis, and Sukru and I are seeing more and more of this patient. Chu And that is a consequence of obesity? Strazzabosco Yes, of the metabolic syndrome. Emre That is correct. Chu In terms of age, what group is at highest risk for developing liver cancer? Emre Based on our estimation, and as Mario indicated, that after receiving or contracting the disease and viral diseases, the development of cirrhosis, and for example, hepatitis C, takes somewhere around 20 years, and after you develop cirrhosis, development

of HCC takes time, maybe five to seven years more. Thinking about just the development of cirrhosis, the HCC takes 25 to 30 years. If we assume that they contract the disease somewhere in the teenage years, at 15 to 20 years of age, our population is mostly somewhere between the 45 to 55 age range where we are seeing the HCC more. Chu What are the typical symptoms associated with liver cancer, what should people keep a look out for in terms of symptoms? Strazzabosco Unfortunately, when you have symptoms related to liver cancer, your cancer is very advanced, so what you should do is to take care of your liver and your doctor should be able to identify the risk factors that you may present, so the possibility of a cancer has to be sought after, because if you can see the cancer when it is small, there are many things that can be done. If you wait until the cancer causes portal vein thrombosis or ascites...10:23 into mp3 file <http://www.yalecancercenter.org/podcast/dec0609-treat-liver-cancer.mp3> Chu

And ascites, can you define ascites for our audience? Strazzabosco It is the presence of fluid in the peritoneal space in your abdomen, outside of the abdomen. Chu So their belly would get a little bit bigger and uncomfortable? Strazzabosco Yes, there would be progressive increase of abdominal girth. Emre I would like to add a couple of things to what Mario said, it is true that if cancer gives symptoms that means that it is very extensive disease and there might be some dull abdominal pain, sometimes we can see development of jaundice or a yellowing of the eyes, and sometimes extreme pain can occur, and we do see ascites or accumulation of the fluid in the abdominal cavity secondary to the cirrhosis, not related to the hepatocellular carcinoma or liver cancer, and if someone does not have a cirrhosis, the development of ascites can be attributed to development of hepatocellular carcinoma. The point we are making here, as Mario said, is we have to look after these patients very carefully, monitor them, I am talking about cirrhotic patients, because we do know that sometimes, along the course of cirrhosis, they are going to develop hepatocellular carcinoma. Screening programs are extremely important in order to diagnose hepatocellular carcinoma early so that we can do something about it before the cancer gets out of our hands and spreads all over the body. That is our aim at this point while we are dealing with cirrhotic patients, just to follow them very carefully and probably every three to six months doing imaging studies and sending what we call tumor markers, or alpha fetoprotein, which is a specific tumor marker for hepatocellular carcinoma, and if we see any imaging study inconsistent with hepatocellular carcinoma, obtaining liver biopsies, and meanwhile, we have different techniques that we are going to discuss later on, to ablate these tumors or eradicate them that we can help them survive for a longer time. Strazzabosco There are actually some recommendations that have been developed by the liver societies both in Europe and here, so if you know that you have some of the risk factors, maybe you are infected with hepatitis B, then you should look for the presence of liver cancer by periodic imaging, even if you are not cirrhotic. If you have hepatitis C, or you are overweight, and you are drinking, then your doctor should try to understand when and if your disease is becoming chronic and cirrhotic, because from that point on, the risk of developing a cancer is 5% per year; therefore, we do not

call it screening, but oncologic surveillance, at least with alpha fetoprotein an ultrasound every six months is warranted. That is the only thing that will let you find the cancer still in a treatable stage. Chu Time for us to break for a medical minute, you are listening to Yale Cancer Center Answers14:02 into mp3 file <http://www.yalecancercenter.org/podcast/dec0609-treat-liver-cancer.mp3> and we are here in the studio this evening with doctors, Dr. Sukru Emre and Dr. Mario Strazzabosco. Chu

Welcome back to Yale Cancer Center Answers, this is Dr. Ed Chu and I am joined this evening by Dr. Sukru Emre and Dr. Mario Strazzabosco from Yale Cancer Center. We are here talking about the approach and treatment evaluation of patients with liver cancer, and before the break we were talking about how important it is to have very careful follow-up of patients who have chronic liver disease. Mario, I will start with you, who would be the key person to oversee the follow-up of a patient with chronic liver disease? Is it a primary care physician, or would it be someone like yourself who is a liver specialist, also known as a hepatologist? Strazzabosco This can be done by either. The primary physician should know that the patient with advanced liver disease should be screened every six months for the presence of liver cancer, as we said earlier, with an ultrasound of the abdomen and the liver and the tumor marker which is called alpha fetoprotein. However, I would recommend sending to the hepatologist, patients that are known to have liver disease, because we actually have designed our practice and our clinic to care for this aspect. It is sometimes not very easy to understand when the moment is in which chronic hepatitis actually becomes liver cirrhosis, which is something much more severe, but can happen without any symptoms at all. Something changes in your liver and will not show clinically for a long time, but the risk that comes with this evolution, that may or may not happen, less than 20% of patients that are infected with hepatitis C actually develop cirrhosis, so there is a lot that your hepatologist or the primary care physician can do before to prevent the cirrhosis and when you are cirrhotic to understand what the risk is.17:04 into mp3 file <http://www.yalecancercenter.org/podcast/dec0609-treat-liver-cancer.mp3> Chu

So once liver cancer is diagnosed, what is the process that is involved in terms of staging the patient to see whether or not it is local, confined to the liver, or has spread? What are the different stages of liver cancer, maybe Sukru you can help us with that? Emre When we diagnose the tumor, first of all the size of the tumor is really important in order to stage the tumor, and the second thing is the number of tumors. The third thing is whether the tumor is opening to any major vessels, and we look at whether there is any tumor outside of the liver and that includes lymph nodes around the liver, bones, and the lungs, and we have to check whether they have any lesions there or not. So, based on looking at the size of the tumor, we stage the tumors to four stages; stage I is tumor less than 2 cm; and if there is more than one tumor and the size is less than 3 cm, or one tumor size up to 5 cm, that will give us stage II or T2 criteria; stage III may indicate that the cancer is composed of several large tumors, or the cancer may be one large tumor that has grown to invade the liver's main veins or to invade nearby structures such as the gallbladder, and

stage IV tumors indicate that the liver cancer has spread beyond the liver to other areas of the body. Chu Mario, what are the different treatment options that are available to us once the liver cancer is diagnosed, once the staging evaluation has been done? Strazabosco The treatment options actually depend strictly on the stage of the tumor, and this is a very peculiar tumor, different from many others, because it is a tumor in a failing organ. There are oncologic criteria and also functional criteria. The liver of the cirrhotic patient is not working very well, so that is a big limitation to the amount of options that you have. When we stage the disease, we try to combine the oncologic extension of the disease, which means size, number, metastasis, with the assessment of liver function. Every doctor who sees the patient with a tumor would go through a mental flow chart. First of all he would ask himself if this patient is cirrhotic, yes or no? And Sukru will this explain later; there is a dramatic change in your option of what to do. Secondly, can the tumor be resected by the surgeon? And if not, what kind of alternative treatment can the patient sustain? And this really depends on the function of the liver. For example, you may have a small tumor that could be addressed by different means, but in a patient with a functional status that is so compromised your only option is actually to transplant the liver. On the other hand, you may have a patient with a little bit of a larger tumor and of very well preserved function, and this patient could be better served by resection eventually or other intervention. This is the assessment that is made every time, and is an assessment that requires multiple competences. That is why all these patients are discussed in a multidisciplinary board that includes hepatologists, surgeons, transplant surgeons, surgical oncologists, pathologists, and medical oncologists, all these specialties are gathered and discuss the specifics of each case.21:58 into mp3 file <http://www.yalecancercenter.org/podcast/dec0609-treat-liver-cancer.mp3> Chu So at Yale, Sukru, just to expand a little bit, when you see a patient newly diagnosed with liver cancer, you have this entire team of doctors that Mario was discussing provide their individual expertise, perspectives, and then come up with a game plan for the patient? Emre That is right, to explain it a little bit more, at our multidisciplinary liver cancer meeting, we have diagnostic radiologists, interventional radiologists, hepatologists, and medical oncologists, surgeons, and social workers, coordinators, and support staff as well, and we all meet together. Each case is discussed in detail and then options are discussed, and if someone has very minimal liver reserve, and the tumor is located in the middle of the liver, resection may not be a good option. On the other hand, if a patient has good liver reserve, what we called Child A cirrhosis or compensated liver cirrhosis, and a favorably located tumor, then resection might be an option. The other option we should talk about is with our interventional radiologists, and they do other ablation techniques, one technique is called radiofrequency ablation, in a way it's an ultrasound-guided approach and we get into the tumor and we can create very high heat in the tumor and we can cook the tumor, or we can freeze the tumor; these are different techniques. Also, our interventional radiologists travel via the vessels and they get into either the femoral vein, or arteries, then they travel through the arteries and get into the

arteries feeding the liver, and even get close to the tumor, and we can deliver high doses of chemotherapy in the tumor and then we knock down the vessels, or arteries feeding the tumor, and we can shrink the tumor down and keep the tumor in the liver. This is a multidisciplinary approach. Chu Sukru, since you are obviously an expert in liver transplantation, when would you typically consider transplantation as a reasonable treatment option for patients with liver cancer? Emre For transplantation there are two ways to look at it. If we have a patient with a single tumor, we control this with ablation techniques, and after ablation treatment, if there is no tumor in the liver, there is no reason to transplant the patient. The second issue is if there is a tumor in the liver and also there is cirrhosis and liver disease, the organ allocation system in the United States at this point allocates the organ based on the severity of the liver disease. Meanwhile, we develop some rules for hepatocellular carcinoma, or liver cancer patients. If the cancer meets what we call T2 criteria, which I explained before, and I will say it again, means that one tumor between 2 cm to 5 cm, or up to three tumors less than 3 cm in diameter, then those individuals will be assigned 22 MELD points then every three months they accrue three more points, and eventually their points will go 22, 25, 28, and 31, and they will get the liver organ offers. And I would like to say one thing that is really important because it is very complex topic; organs are allocated to patients directly based on MELD score. MELD stands for Medical End stage Liver Disease scoring system, so if your liver tumor is more than the T2 criteria you may not get the liver transplant through this system, 27:04 into mp3 file <http://www.yalecancercenter.org/podcast/dec0609-treat-liver-cancer.mp3> for those cases, living donor liver transplantation will be a great option for the patients and get the transplant done timely, saving the life. Chu We have seen a lot of advances in the treatment of liver cancer over the years, and Mario you have obviously been involved. In the minute and a half we have left, can you tell us a little bit about how things have evolved? Strazzabosco This is an important question because it lets us also give some good news to our patients. The treatment of liver cancer has changed dramatically in the last 10-15 years and what was previously a death diagnosis, is now a diagnosis with which you can live many years depending on the stage of the diagnosis of course, but we also have multiple approaches. First of all, transplant is now an option; it was not 10 year ago. Second, our interventional radiologist is continuously refining the approach that they can offer to our patients and they can use embolization with radioactive material, drug eluting beads, we do not have the time to go into the details for each of those, and the last development in the last two to three years has been the application of biological drugs, meaning compounds that can block a specific signaling mechanism that drives the growth of the tumor. There are many of these drugs in the pipeline as we say and will be available to patients, and we put great hope in those new non-chemotherapeutic oncologic drugs. Chu It is amazing how quickly the time has gone, and we will have to have both of you come back so we can discuss more about how far we have come in terms of treatment of patients with liver cancer. Thank you so much for joining us this evening. You have been

listening to Yale Cancer Center Answers and we would like to thank our guests, Dr. Emre and Dr. Strazzabosco for joining us this evening. Until next time, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week. If you have any questions or would like to share your comments, you can go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.