Welcome to Yale Cancer Center Answers with Drs Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center, and Dr. Miller is a Medical Oncologist specializing in pain and palliative care. He also serves as the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening, Ken Miller welcomes doctors Wasif Saif and Mario Strazzabosco to talk about liver cancer. Dr. Saif is Associate Professor of Medical Oncology and Head of the Gastrointestinal Cancers Program at Yale Cancer Center, and Dr. Strazzabosco is a Professor of Internal Medicine Specializing in Digestive Diseases at Yale School of Medicine.

Miller Let me start by asking you, what causes cancer of the liver?

Saif There are multiple causes of liver cancer. The most common cause that we are aware of is chronic infection with hepatitis B and C. In addition, heavy alcohol use is a cause for liver cancer. There are other causes which seem to be more prevalent in different parts of the world, particularly people who are exposed to a toxin called aflatoxin. This is related to people coming from Africa with the use of peas. Being obese can also lead to liver cancer and there are some hereditary conditions such as abnormal accumulation of certain minerals in the body that can lead to liver cancer as well.

Miller Let me ask you a related question. There are people out there who have hepatitis B or hepatitis C. If someone has a history of hepatitis C, are they at a higher risk of developing liver cancer?

Strazzabosco Absolutely, but let's take a step back. First of all we need to distinguish what cancer of the liver we are talking about.

Miller Okay.

Strazzabosco There are mainly two types of liver cancer, one originates from the hepatocyte, a bulk of cells that make the liver, and one originates from the biliary tree. The cancer that comes from the hepatocyte is called hepatocellular carcinoma, or hepatoma, and all causes of chronic liver disease may ultimately lead to cancer, however, we can define the patients that are at highest risk. First there are the people that have hepatitis B virus infection. This is a direct oncogenic virus that has been recognized and it can lead to liver cancer even in patients that do not have liver cirrhosis. On the other side we have patients with hepatitis C virus. In this case, although the virus does not seem to be directly oncogenic, the resulting liver disease can put them at higher risk. However, an important point to make is that the hepatitis C virus is not the only cause of liver disease that can lead to cancer. If you are just obese, you may not get liver cancer, but if in addition to

that, you drink and you have hepatitis C virus, then you have an acute relation of risk factors that ultimately leads to a very high risk of developing liver cancer.

Miller Along those lines, what is it about those diseases of the liver? On one hand it's a virus that actually may cause the cancer directly, but the other conditions, how do they lead to cancer. What is your theory on that?

Strazzabosco As you correctly say, it is a theory. Advanced liver disease is a combination of three main conditions. Liver cells are dying, liver cells are being replaced by regeneration and there is an ongoing inflammatory environment. All these activities go on for 20 years and at the end will lead to genomic changes of instability and ultimately the development of cancer. It is a stronger generative condition that is happening in an inflammatory environment. All the inflammation related oncogenic mechanisms are in action here. It is important to remember that it takes a long time to develop this cancer in a patient.

Miller With that in mind, if someone is in one of those risks groups, how do you make the diagnosis? Is there screening that you would recommend for someone who has a history of hepatitis?

Saif There are definitely screening guidelines from different National Associations. The first thing is, of course, a history. A history and a physical are key. The second thing is the education of the patient. The third is recognizing the high risk patient and screening them doing an ultrasound as well as a blood test called alphafetoprotein, which is a chemical that you can measure in the blood. This should be done periodically and the patient should be watched for clinical signs of chronic liver disease that can also be of concern for liver cancer.

Strazzabosco Education of the patient and all the physicians as well is important.

Miller Okay.

Strazzabosco These people are recognized as patients at risk. Guidelines mandate a six month oncologic surveillance with liver imaging. The kind of liver imaging clearly depends on your own particular local situation, and alphafetoprotein, although it is important also to point out that only 30% of patients will develop a rise in this oncogenic marker. So, don't stop with the alphafetoprotein. It is useful in some patients but it is not the whole story. The real basis here is to do repeated imaging at 6 month intervals in any patient recognized at high risk for liver cancer.

Miller This will be MRI scans or CAT scans? What's the gold standard?

Strazzabosco It depends on your local situation. If you are in Europe, for example, ultrasound would be the gold standard. There are centers that prefer to do repeat

CT scans or MRIs in patients that are identified for some reason to be at higher risk.

Miller What symptoms might a patient with liver cancer have that would make them suspicious?

Saif It is very important for listeners to understand that the symptoms of liver cancer are somewhat nonspecific. When I define the symptoms for liver cancer, I define them under three groups. The first group is constitutional or generalized symptoms that may include loss of appetite, weight loss and feeling tired. The second group of symptoms is local symptoms; the patient may feel a mass in the right side of the belly under the ribs or tenderness or pain in that area. The third group of symptoms is called liver associated symptoms. These may include nausea, vomiting or jaundice. In addition to these symptoms, a patient who has a chronic liver disease could also have a stigmata of some symptoms, which are related to the liver disease itself.

Miller How common is liver cancer?

Strazzabosco It depends on the geographic area. Here in the United States we would say there is a lower incidence area, but this will be changing due to migratory flexes and so on. Unfortunately it is rising and it has doubled in the last 20 years. It is now around 5 to 6 per 100,000 people. I can give you some figures from Connecticut that we retrieved recently, in the year 2000 there were 160 deaths related to liver cancer in one year.

Miller And that number is going up?

Strazzabosco The number is going up.

Saif In the United States, if you look at the statistics, unfortunately we see about 18,000 cases per year. Worldwide the number is over 1 million patients. Worldwide this is the fifth most common cause of cancer.

Miller I was going to add to that that there are about 11 million cancer deaths worldwide every year, so 1 million being from hepatoma is really a huge number.

Strazzabosco It is third most lethal cancer worldwide. The survival is not very good. Early diagnosis is important, as in every other oncologic disease, but here it is really important. We have multiple ways to address the cancer early on in the liver, but in that phase, the cancer will be silent. There would be no sign.

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Miller And if it's caught early on, that would be the situation where the patient would have the best chance of care.

Strazzabosco This is where we have an armamentarium of options that are actually improving the prognosis of patients, but the key is to have a high level of suspicion and do the oncologic surveillance and diagnose the cancer early.

Miller What are the stages of liver cancer?

Saif From the oncological point of view, we divide liver caner into 3 stages. I will try to make it very simple and also follow them scientifically. One is local resectable liver cancer. In medical terms, we are looking at a tumor which is selected T1 and T2. Why I am saying selected is because the location of the tumor and also the proximity to the blood vessels and other organs is very important. The second stage is a locally advanced unresectable tumor, where the tumor is based within the liver area, but because of the location or because of the concomitant diseases such as cirrhosis, it has become unresectable. The third stage is advanced liver cancer, when the patient has disease with lymph node involvement or other distant areas such as the lungs and bones.

Strazzabosco That is the oncologic classification. One of the reasons why this is a very interesting field is because it is in between internal medicine and oncology. 90% of liver cancer in our area is on top of cirrhosis. It is a cancer that occurs in a failing organ, and that is why Wasif and I are planning to do a clinic together. This patient has a severe organ insufficiency, so the hepatologist actually tries to use a combination from an oncologic staging and a functional staging, because whatever you do you are going to be bound by what that liver can stand.

Miller It is interesting because what you are posing is a different situation, for example, then what I face treating women with breast cancer. For the most part these are healthy women. We are using preventative therapy, but these are people that are very ill with liver disease.

Strazzabosco Some of them are cachectic, some of them have kidney failure, some have the complication of cirrhosis, ascites etc., and so when you plan a therapeutic strategy on a single patient, you have to take these into account. We use a combination of oncologic and internal medicine classification which is called the Barcelona Liver Clinic staging system, which tries to combine this dual personality of cancer and recommend treatment. This is another reason why this is the only center that can offer a multidisciplinary and a multimodal approach to the cancer.

Miller I want to jump ahead. We have an E-mail from a patient who writes that they have advanced liver disease from cirrhosis, and also were recently diagnosed with hepatoma. They are looking into a liver transplant. This is sort of an extreme

situation, but maybe not uncommon for you, but is liver cancer and liver disease curable by transplant?

Saif — That is a very good question. I will give part of the answer and then ask Mario to help me out. Liver transplant is one of the potential ways of curing liver cancer and the 5 year survival has reached, in some cases, to 60% to 70%.

Strazzabosco — Liver transplantation is the curative treatment for liver cancer, but there are some caveats. Unfortunately, not all patients can undergo transplantation because if the hepatoma exceeds a certain staging, it will come back in the new liver. We have a strict classification for assigning patients to liver transplantation, but those that can be assigned are the patients with early cancer. The survival is amazing. Also, in patients that have severely reduced liver function, any other option might be futile short of transplantation.

Miller — We would like to remind you, our listening audience, to E-mail your questions to canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about liver cancer with Dr. Wasif Saif and Dr. Mario Strazzabosco.

Medical Minute

The American Cancer Society estimates that in 2008, there will be over 62,000 new cases of melanoma in this country and about 2400 patients are diagnosed annually here in Connecticut alone. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths, but when detected early, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the Yale Cancer Center to test innovative new treatments for melanoma. The patients enrolled in these trials are given access to newly available medicines that have not yet been approved by the Food and Drug Administration. This has been a medical minute and you will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Miller — Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am here with my guests Dr. Wasif Saif and Dr. Mario Strazzabosco, discussing the latest research on liver cancer. We were talking a minute ago about the patients who have liver transplant for hepatoma cancer of the liver, but let's talk about patients with early stage disease. If someone comes to Yale, who are they seen by. Who is their team?

Saif — That's a very good question, and I think Mario tried to give the background for it earlier. Liver is a heterogenous disease. It has multiple causes, plus this disease can be very different in different people based on their background with liver

disease. The different treatment modalities are a major challenge that we have when treating patients. How we treat these patients is done through a multidisciplinary tumor board where the patient is discussed among all the modalities, including internal medicine, gastroenterology, a liver transplant surgeon, intervention radiologists, a radiologist, a pathologist and a medical oncologist. The whole team sits down together and makes the best plan for the patient based on the most recent evidence available from the medical literature and our experience.

Strazzabosco The patient can be a referral from multiple sources, and so we have implemented a multidisciplinary board. The patient is discussed among that team. Because of the situation in many places, and literature shows the results of this, patients are being treated in a very uneven way throughout the different countries. Because of this there was a direct referral to certain providers of a particular technique, which is good in a way, but the different masses and specific situations of every patient are so intricate, that only a multidisciplinary discussion can really lead to the best allocation. What we do is we put the case on the table and everybody has their own input. At the end, we reach a panel decision that is the best indication of the way to go. The patient may come to us through radiology and end up in surgery, or come from a transplant where the transplant cannot be done, and end up in oncology, and so on and so forth. It is important that the public understands that this is a disease that can be managed, but only in a few hospitals that provide the whole range of care for transplantation to new biological agents for the medical treatment of this disease. Anything short of that will actually prevent a complete decision.

Miller It is a wonderful reminder that it is obviously a complex disease and getting multidisciplinary care is very important. I want to ask you about some of the latest techniques in treatment. What is transarterial chemoembolization?

Saif Transarterial chemoembolization, which is abbreviated using the term TACE, really means regional chemotherapy. What we do is we place a catheter into the hepatic artery and this is based on very good science because there are two blood vessel supplies to the liver. One is the hepatic artery that supplies the tumor, and the second is the portal vein that collects blood from the stomach and the intestine and supplies the normal liver tissue. So, by placing a catheter in the hepatic artery, we give chemotherapy with the substance that blocks the blood supply to the tumor. By blocking the blood supply to the tumor, oxygen and other nutrients do not reach that tumor and that leads to the shrinkage or the death of cells of the tumor. TACE is a very effective regional therapy and some series have shown that by doing this kind of therapy you can give a five-year survival for 25% to even 40% of patients. In people who have locally advanced disease and are not amenable to surgery, transarterial chemoembolization could be a very effective way of treating them.

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Miller Mario, let me ask you, what is radiofrequency ablation?

Strazzabosco Radiofrequency ablation, also called ablative therapy, is a very effective local regional treatment for liver cancer. It is usually performed transcutaneously, but in a few centers it can also be performed through a laparoscopic approach. The idea is to kill the tumor by physical means. In the case of radiofrequency ablation, a needle is inserted into the tumor. This needle branches out to the tumor and then catches the tumor and literally cooks its like it's in a micro-oven that creates an atomic affect and the tumor is actually cooked. For patients in which this cannot be done, because, for example, the tumor is too close to some other organ or vital vessels, the radiologist can actually insert a needle and put pure alcohol inside that will kill the cells.

Miller I want to ask you about systemic therapy. Wasif, what is the latest in terms of either chemotherapy or new drugs, and what are you working on?

Saif The good news is that finally the ice is broken on the peak of the problem that we are dealing with, ACC. A drug called Nexavar, or sorafenib, is a small molecule drug that is given by mouth that is fixed on the blood vessel formation pathway in the cancer formation and has been approved by the FDA for liver cancer. We are developing further drugs. In addition to this, at the Yale Cancer Center we also have a drug which can be given if you fail sorafenib. Now we are in the right direction to also develop systemic therapy for these patients. The next questions are going to be answered as a multimodality discipline among each of us, as to how to use those drugs in patients who have gone for liver transplant or who are waiting for liver transplant, and what should we do with these drugs if we combine them with radiofrequency ablation? This is becoming a more and more exciting time and finally I can see that there is going to be something good that happens in the treatment of liver cancer.

Miller Which is absolutely exciting.

Strazzabosco Let me put this into context, because this is good news for the patients actually. In respect to 10 years ago, there is a lot that can be done for patients who are diagnosed early enough. There is a way to allocate each patient to the treatment. The best treatment is still liver transplantation. But for those who for many reasons cannot undergo this procedure, we have other means to treat the patient. The problem is really to allocate the patient to the proper treatment, and this can be addressed through this multidisciplinary work. We had experiences with radiofrequency ablation, for example, where out of 100 patients, 70% of them are still alive 5 years after. One of the problems is that the tumors tend to recur, so one of the things that we need to address scientifically is how to use these new drugs to prevent the recurrence in the tumor. We know how to treat the first one.

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Miller Yes.

Strazzabosco But the second one is the problem.

Miller If a patient has a liver transplant, or we resect a tumor in the liver, how might these drugs sorafenib or Nexavar that you are mentioning help?

Saif Right now the whole focus internationally is looking at how to use these drugs in those scenarios. First of all safety is very key, and secondly the efficacy. Right now, we as the national leaders and international leaders, are looking at producing new clinic trials to see how these drugs can be used best in that context, and hopefully, the future will bring out the answer of how we can use these drug in the best possible way.

Miller Can you combine this drug sorafenib with chemotherapy?

Saif That is an excellent question. Ken, just 2 months ago at the International GI Conference study, it was presented combining sorafenib with doxorubicin, and the combination of those two drugs together seem to enhance the efficacy. We are also presenting another study at the International Symposium of American Cancer Society two months from now where we will present the data on combining an oral chemotherapy called capecitabine, and we are very excited about the results. We are on the right path. We know we have to hold each other's hand and now we have the active agents to play with. I really hope that this will bring a good future for our patients.

Miller What are some of your goals for your program in the next few years?

Strazzabosco The first goal is to have this combined clinic up and running so that patients will receive, on the same day, the oncology, pathology and surgical consult. We also aim to expand the number of clinical studies that we can offer to patients. It is good for a patient if a center can offer clinical studies. Being able to offer studies to patients is also a clinical duty, not only a scientific interest.

Saif I totally agree with you and we both are whole heartedly willing and putting all our efforts in to make this path go forward.

Miller It is very exciting in terms of the progress you are making, and have made already in treating this disease which previously had been extremely difficult to treat. Wasif and Mario, I want to thank you both very much for joining us tonight on Yale Cancer Center Answers. It has been a great program. Until next week, this is Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

26:40 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-04-08.mp3

If you have questions, comments, or would like to subscribe to our podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, we will examine nutrition and cancer prevention with Dr. Susan Mayne.