

Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed and Francine welcome Dr. Wasif Saif. Dr. Saif is an Associate Professor of Medical Oncology and an expert in the treatment of gastrointestinal cancers at Yale Cancer Center.

Chu Our topic for this evenings show is liver cancer. Could you start off by telling us what liver cancer is?

Saif This is a great time to talk about liver cancer because after the last two decades we are now able to develop new drugs for liver cancer. Liver cancer, basically, is cancer of the liver tissue, which in general is a very heterogeneous disease, meaning that it can be caused by many things in different parts of the world. In simple words, it is a cancer of the liver itself, not the ducts passing through the liver.

Chu A lot of times when patients are given a diagnosis of cancer, they are told that the cancer has spread to the liver coming from say the colon, the breast, the lung, or pancreas, but what we are talking about today is cancer that comes primarily from the liver itself.

Saif That is a very important distinction that should be made in these patients; whether the cells which are giving origin to the cancer are coming from the liver itself, or from other sites such as the colon or pancreas.

Chu Is there another name for that, a fancier term?

Saif A hepatocellular carcinoma, in simple abbreviation you will also see the term HCC, which is commonly used for this cancer.

Foss What are the major causes of liver cancer and how do patients know whether they are at risk for this?

Saif The causes for liver cancer can be divided into different groups. One is acquired causes, the second is inherited causes, and the third is environmental causes. The acquired causes are the ones which are caused by the infection with hepatitis B or hepatitis C virus. People who are obese can also develop cirrhosis of liver, which can lead to liver cancer as well. The inherited causes

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include Wilson's disease, which is a disease of the metabolism with the disturbance of copper. In addition, people could also have another disease called hemochromatosis. This is a disease where the patient has abnormal genetic formation that mishandles the iron deposition in the body. There is another syndrome, alpha-1 antitrypsin deficiency as well. Environmental factors are betel eating in the Asian countries and also use of aflatoxin, which is a poison, which can lead to HCC or liver cancer in Africa, where people are eating raw peanuts.

- Chu Wasif, here in the United States what is thought to be the most common cause of liver cancer?
- Saif Right now the top cause of liver cancer, in about 60% to 70% of cases, is due to hepatitis C, followed by hepatitis B, and alcohol abuse. Unfortunately, with today's dietary habits, NASH, which is Nonalcoholic Steatohepatitis, or obesity-induced liver disease, is at a higher increasing incidence in the United States, which is a nightmare for us because this can cause liver cancer in the future.
- Foss A lot of people have hepatitis, or fatty liver, how do patients know whether they are at risk for liver cancer? What are the major symptoms that a patient would have?
- Saif The main thing is that, unfortunately, patients with hepatitis B have a hundred fold increased risk of developing liver cancer. At the same time, for patients who have hepatitis C, about 30% to 50% of those cases develop cirrhosis, and one-third of those develop liver cancer. When these people have cirrhosis of the liver they develop liver dysfunction, which can manifest in different ways. These patients could have swelling of the body, a decrease in appetite, and sometimes they can develop high levels of hemoglobin, called polycythemia. But when these symptoms start changing, that is a sign that something is happening. In these patients it can take about 10 years or more to lead to development of cancer.
- Foss How is the disease diagnosed?
- Saif The disease is diagnosed in different ways. The first is a clinical picture. Patients can develop weight loss, fever, and lack of appetite. The second is the picture we see in the blood. Of course these patients have liver dysfunction, which means there could be jaundice, or they could have liver enzymes going up. In addition to that, there is a special test called alpha-fetoprotein, which is abbreviated as AFP. This is a tumor marker that can rise in patients with liver cancer. Of course, as with other cancers, we have imaging modalities available. MRI, which is Magnetic Resonance Imaging, is very similar to the CAT scan and is the standard therapy used to diagnose liver cancer on imaging. Finally, the diagnosis has to be made with a histological diagnosis by doing a biopsy of the liver cancer cells and looking at them under the microscope.

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- Chu You mentioned a moment ago that hepatitis C and hepatitis B are the two most common risk factors for developing liver cancer in this country. If someone has a diagnosis, as Francine suggested, obviously they are going to look out for symptoms, but would you want to screen for those patients to see if they might have early stages or early forms of liver cancer?
- Saif That is exactly true Ed. We have standardized guidelines for those patients. We always like to vaccinate patients with hepatitis C to make them immune against hepatitis B. At the same time, these patients need to have regular follow ups with their physicians where they should have serial ultrasounds as well as look in the blood for the alpha-fetoprotein, the blood test I mentioned earlier. We have guidelines to move forward as we see the increase in the size of those lesions, starting from less than 1 cm to go beyond 1 cm.
- Foss Can you talk about the patients who have cirrhosis, or are using alcohol, and patients who have fatty liver? To what degree can they influence their chance of getting liver cancer in the future by modifying some of these factors now?
- Saif This is really a disease that I always say is to some extent preventable. We have to understand that this is a disease that alcohol abuse can lead to; at the same time, if everybody gets vaccinated for hepatitis B, it can also prevent this disease. Unfortunately, right now for hepatitis C we do not have a preventive vaccine available. However, there are many other reasons people get this infection such as a blood transfusion that is not screened for hepatitis C or B, or a patient getting an organ transplant in another part of the world. Luckily in the United States, most of these procedures are performed before getting those transplantations or transfusions. Definitely by modifying our dietary habits, trying to cut down the intake of fat, and regular exercise, we can prevent and decrease the incidence of this monster disease.
- Chu Can anyone in this country get vaccinated against hepatitis B?
- Saif It is really based on the awareness. We definitely need to bring more public awareness. I can tell you that among all the people in the medical field, in general, they are required to have the hepatitis B vaccination. I believe that now it is becoming a more common trend to give the hepatitis B vaccine when kids are first born. I am hoping that with this new trend it will lead to decreased incidence of this cancer in the future.
- Chu What is really fascinating to me is that in Taiwan, liver cancer has been one of the major cancers and cancer killer for many, many years. About 15-20 years or so ago they instituted hepatitis B vaccination for kids and it's amazing. They have already seen the incidence of liver cancer fall dramatically.

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- Saif I think it is a very positive lesson for all of us to learn that by having the vaccination it will prevent a lot of cost in the treatment of this cancer and we will save many lives.
- Foss Wasif, can you just comment on hepatitis C? I understand that there is not a vaccine for it. What can we do about that as a risk factor?
- Saif That is a very interesting question. Right now there are a couple of things that we can do for these people. There is an immunotherapy called interferon. The interferon is an injection that has been tested and used and can delay and prevent the development of cancer and cirrhosis in these patients. At the same time, some antiviral antibiotics, which also have been used for the treatment of HIV, have been under exploration to help this disease, to prevent the development into cirrhosis and liver cancer.
- Foss If you are on one of these treatments for hepatitis C, and your virus is silent, are you still at risk for liver cancer?
- Saif As long as we keep the virus at the low risk and we are not letting the liver become more damaged, we definitely can delay, and in some cases prevent, the development of liver cancer.
- Foss You mention that toxins or chemicals might also be a risk factor. There are lots of people out there that may have worked in factories or been exposed to various chemicals at different points in their lives, should they be worried about liver cancer?
- Saif There are a multitude of toxins thought to cause liver cancer. A few years ago there was a concern about people using anabolic steroids, which can cause liver cancer. Some chemical exposure such as ethylene glycol can also cause damage. In addition, there was some concern about using oral contraceptives, but none of those studies have shown a statistical association of these exposures to the development of liver cancer. However, the use of raw peanuts that can lead to the poisoning of aflatoxin is the only environmental factor that has been well established to cause liver cancer.
- Foss We are going through this peanut scare in the United States, can you talk about that? Should we worry about our peanut butter and our peanut products right now?
- Saif I think right now the only concern, as you know from the news, is Salmonella. We really need to know from where these peanuts are coming from, keeping in mind that there are three major sources of peanuts coming to United States. One is of course Africa, but most commonly we get from South America, and the third source is China. I think it is also based on where they were cultured, where they were grown, but I think right now there is no scare. Acute use, one

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or two times, of those peanuts will not lead to liver cancer. It is the chronic use of those things that can accumulate and cause liver damage.

Chu Once the diagnosis of liver cancer is made, who should that individual seek for medical attention?

Saif This is a stepwise pattern that involves a lot of physicians. This starts from the primary medical physician, or the PMD, or the clinician that has been seeing the patient for a long time. When these patients are diagnosed with hepatitis C or B, sometimes they end up having the involvement of a hepatologist. A hepatologist is the gastroenterologist physician who specializes in liver disease. When it comes to the diagnosis, of course, that includes the involvement of a medical oncologist. In addition, we need a radiologist who will be looking at the MRI or other CAT scan reports, and we also need a pathologist who will be confirming the diagnosis. It requires the involvement of many people, as we want to make sure before we make the decision for this patient's treatment, that we confirm the diagnosis.

Foss How do you do a biopsy on a patient with liver cancer?

Saif That is a very, very challenging situation. Unfortunately, most of the patients with liver cancer have coagulopathy. Coagulopathy, in simple terms, means that these patients have thinned-out blood due to the lack of proteins produced in the liver, and they can bleed. At the same time, if these patients have cirrhosis, which is the fibrotic development of the liver tissue which can also lead to the enlargement of the spleen, and unfortunately, the enlarged spleen also squeezes their platelets and they have low platelets, which is a cell component that reduces the risk of bleeding. That is the reason we have to be very careful doing a biopsy on those patients, which is mostly done by a fine-needle aspiration. However, we have guidelines that can prevent a biopsy on those patients if we have certain criteria fulfilled.

Foss Do patients with liver cancer develop metastasis like with other cancers?

Saif That is true. Liver cancer can metastasize to many areas. It can go to the belly and cause fluid in the belly, it can go to lymph nodes, it can go to lungs, and it can even go to bones; in very rare cases it can go to the brain.

Chu Do you typically do CAT scans, or other x-ray imaging studies, to make sure that the liver cancer has not spread beyond the local area of the liver?

Saif That is exactly correct Ed, and if we are concerned about bones we also do a bone scan, which is a nuclear medicine test.

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Foss Thank you very much Wasif. We are going to take a break now. You are listening to Yale Cancer Center Answers and we are discussing the treatment of liver cancer with Dr. Wasif Saif.

MedicaMinute

It is estimated that over 2 million men in the US are currently living with prostate cancer. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests; a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. Patients enrolled in these trials are given access to experimental medicines not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Wasif Saif, a medical oncologist at Yale Cancer Center. Wasif, we talked a little bit about liver cancer, let's focus our discussion on the treatment options for this disease. Can you talk a little bit about the treatment for liver cancer?

Saif The treatment options can be divided into many groups. The reason I bring up the group is because it is very important to understand that bringing the different groups together will help us know how many people are involved in the treatment of liver cancer. Of course, surgical dissection is the gold standard and the only curative potential for these patients. Patients can also be given local therapy which can include modifying the temperature delivered to the cancer cells causing the damage. There is also something called TACE, that we will discuss, chemotherapy, and finally liver transplantation.

Chu The surgery that you talk about, is that performed by a general surgeon or someone who specializes in gastrointestinal cancers, or liver cancers specifically?

Saif That is an extremely important question Ed, and it is really important for my listeners, and my patients and their families, to know that this is a surgery where you want to go to a specialized person who is well trained and well experienced at performing liver surgeries in patient with liver cancer. Patients must go to a liver specialist who is specialized to do those things because of the complexities in the liver structure due to the cancer and underlying liver disease.

Foss What if a patient cannot have surgery, what if the tumor is inoperable?

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- Saif That is a big question that I would like to piece into different portions. The first thing is that if somebody cannot go for liver surgery, because they have multiple areas of disease and cirrhosis, then those patients are candidates for liver transplantation, if they have no disease outside the liver. If the patient has localized disease, but are not surgical resection patients due to cirrhosis, and the disease is limited to one or two lobes or different areas, those patients can go for a local therapy that can include radiofrequency ablation or transarterial chemoembolization.
- Chu What is radiofrequency ablation?
- Saif Radiofrequency ablation is trying to heat up the tissue cells in the cancer part of the liver by using single, or multiple, electrodes. By virtue of that you can kill the cancer cells.
- Chu So that would be good if you had isolated tumors within the liver?
- Saif That is exactly true. For patients that have isolated tumors, in particular patients that are not amenable to surgery, or patients with cirrhosis where we think that surgery may not be amenable, radiofrequency can bring out good results. To bring some historical perspective of radiofrequency ablation, going back a few years ago this was not a very common procedure. In Japan, they did an ethanol injection procedure, which was able to reduce the cancer in about 40% to 50% of the cases. This is a recent technology that is a great alternative to ethanol injection into the liver cancer.
- Foss You mentioned radiofrequency ablation, and also a procedure called TACE, or embolization of the tumor. Can you tell us how those are different and what is TACE?
- Saif TACE stands for Transarterial Chemoembolization. The liver has two blood supplies, one is the portal vein that supplies the liver parenchyma, or liver cells, and the second is the hepatic artery infusion that supplies blood to the tumor. By obstructing the hepatic artery, we can lead to the necrosis of vascularized liver tissue. We can do this procedure with two technologies. Most commonly, we use gelatin-like foam that obstructs the artery and leads to the death of the cancer cells. In some cases, we also include chemotherapy, which is given through the artery after blocking it so that we not only cause damage to the tumor by depriving it of the blood supply, but leaving behind chemotherapy will cause further damage to that cancer cell.
- Foss That sounds fairly complicated. How long does the patient have to stay in the hospital for that kind of a procedure?
- Saif It is based on the experience of the center. At a tertiary cancer center like Yale Cancer Center, we do this procedure very commonly. It is done by intervention radiology after we discuss the case in a multidisciplinary tumor board. This procedure can be done where the patient may only have to

stay for couple of days. This procedure is getting much easier with the expertise we have in our hands here.

Chu Wasif, you mentioned liver transplantation. Many, many years ago, for those sports fans out there, Mickey Mantle unfortunately had liver cancer. There was a lot of publicity about him getting a liver transplantation, that unfortunately, did not help him, but who are the types of patients that are most appropriate for liver transplantation?

Saif The patients that can qualify for liver transplantation are patients who are surgical candidates, except they have cirrhosis of the liver. These are the patients who do not have any extrahepatic disease, or macroscopic involvement of the blood vessels.

Foss Does it make any difference whether you have hepatitis B or C, as to whether you are a candidate for liver transplant?

Saif Not really. The concept of liver transplant is a very neat one. In reality, liver cancer is the only tumor, the only solid tumor, where we have a very reasonable rationale and success for doing transplantation by replacing the liver with a donor liver. Not only are we able to cure the cancer, but we are also able to improve dysfunction, which was the reason causing the cancer in that patient.

Foss We hear a lot about the shortage of organs for donation, can you tell us how long it usually takes to get a liver transplant?

Saif There are a lot of issues. First of all, it is a supply basis issue, and second it is also cultural differences. In the United States, the average time for a patient to get a donor liver could be from 8 months to 2 years time, and unfortunately, right now, the current dropout incidence is about 20%. Keep in mind that there are two kinds of liver transplants which are done in different parts of the world. One is the cadaveric, which is from a dead person, and second is the living donor. Keep in mind that there are some cultures, some religions, where patients do not want to get a cadaveric liver transplant. Right now it is really a challenging situation to get the right patient at the right time, and of course a patient has to be on the waiting list that reminds us that we have to create some kind of intermittent treatment procedures for these patients to control the cancer.

Chu What has the experience been at Yale Cancer Center with respect to liver transplantation?

Saif As you know, we have outstanding folks who joined Yale Cancer Center a few years ago. Dr. Sukru Emre came here from the New York area, and we also got Dr. Mario Strazzabosco from

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Italy. We have a very robust team and are launching an outstanding program. We are hoping that we will be one of the most recognized, world-renowned centers for liver transplant.

Chu One of the real breakthroughs is that a new target therapy was recently approved to treat liver cancer. Can you tell us a little bit about that?

Saif That is exactly where I started my first discussion today, that this is an exciting time, and the right time to talk about liver cancer. The reason is that we now have Nexavar, which is also called Sorafenib. It is a small molecule target drug, which is approved by FDA for the treatment of liver cancer. This is a pill form drug, so patients take it by mouth, and this is a drug that works by working on two targets. It decreases the blood supply to the tumor. At the same time, there is a growth factor pathway in the cancer cells, Raf pathway, and this drug also inhibits that growth factor pathway and decreases the tumor growth. This drug was used in an international study called SHARP, and that study showed that patients who received this drug have a 44% increase of survival compared to no drug.

Foss Would a patient get this drug first as part of their initial therapy for liver cancer, or would they get it later on?

Saif This is an extremely important question, what is the best treatment for a patient? This is, again, decided by a multidisciplinary tumor board, because we always want to give the best to the patient. We know that surgical resection and liver transplant are the best treatment options for those patients. If those patients have unresectable localized disease, or advanced disease, and if those patients are not candidates for local therapy, surgery, or liver transplant, then Sorafenib is the drug of choice for these patients.

Foss What about patients that do not have outpatient prescription coverage? This is a big problem nowadays and I am wondering about some of these new drugs that are very expensive.

Saif This is a very difficult situation and I think that now, with the current situation, it is going to be even more challenging. As this drug has been approved after working hard with our folks at the cancer center, we have multiple folks who are involved just in helping with this, fighting with insurance companies and asking for different resources. So far we have been quite lucky getting this drug out to most of our patient at Yale Cancer Center.

Chu I have heard that the sponsor of the company that makes Sorafenib, which is Bayer Pharmaceuticals, has some type of reimbursement program.

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- Saif They have sponsored programs for patients who cannot afford it, and they are willing to help those patients get treated for liver cancer.
- Chu You have been very active in developing new treatment regimens for colon cancer, pancreatic cancer, and also liver cancer. Can you tell us a little bit about the types of studies that you have done, and are planning to conduct in the future?
- Saif We are trying to create a robust state of the art cancer center, and the GI program is having a lot of challenges. Why challenges? Because GI cancers, together, are the most common cancers worldwide and we have to work on many cancers; we cannot leave any cancer behind. That is the reason liver cancer is another enemy that we have been fighting. At Yale Cancer Center, we have performed a clinical trial using a Chinese herb medication called PHY-906. This clinical study also used another drug called Capecitabine, or Xeloda, which is a commonly used chemotherapy for many cancers including colon, pancreas, and breast cancer. We combined the two drugs in liver cancer and we presented this clinical data at our international meeting last year and it was very promising to see that the median survival was approaching almost 36 weeks time. In addition to that, we also have conducted clinical studies with other drug such as S-1. S-1 is another oral medication that we have seen very interesting results for with liver cancer, and now we are opening another clinical trial with a drug called TAC-101, which is another drug that works on a cancer receptor antagonist that will be given to patients who have failed Sorafenib.
- Foss It sounds like there is a lot more hope for patients with liver cancer today.
- Saif That is exactly true, and I think that goes to the understanding of the cancer itself. As you know, multiple clinical trials are looking at drugs such as Erlotinib, Sutent, Avastin, or bevacizumab, and other chemotherapies, so after we have realized that we can conquer this disease, we are getting more robust and more targeted in treating this cancer.
- Chu It is quite remarkable because when all of us started our careers in oncology, when we heard about liver cancer, the feeling was that the prognosis was pretty dismal, but I think we have come a long way in a very short period of time.
- Saif This is an exciting time for us, to know that things that were unsuccessful in the past, which were the reason of our failure, now are the reason of our excitement because we have a hope, and this hope is strengthened by what we see in our patients; living longer and having a better quality of life.

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- Foss Can you talk from the point of view of a patient, what resources are out there? Is there a foundation for liver cancer, or other resources that you direct patients toward?
- Saif Right now there are a lot of resources around here. We need to recognize them and try to make them interconnected to each other. As you know, American Liver Foundation also has a chapter in Connecticut. Last year, myself, Dr. Salem, Dr. Mario Strazzabosco, Dr. Sukru Emre, and Dr. Jeff Hollick all gave lectures in the State of Connecticut. We had people statewide come here to talk. People can also go to yalecancercenter.org and that will be able to provide information to patients and patient care providers.
- Chu In the last 30 seconds, Wasif, any last minute messages that you would like to convey to our listeners out there?
- Saif The one thing is to keep in mind that this is a preventable cancer, and we want to prevent it. Do not lose your hope, we are here to help you at Yale Cancer Center and together we can fight this disease.
- Chu Thanks so much for joining Francine and me on the show this evening. You have been listening to Yale Cancer Center Answers. I would like to thank our guest expert Dr. Wasif Saif for joining us. Until next time, I am Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past program. I am Bruce Barber and you are listening to the WNPR Health Forum for Connecticut Public Radio.