Living with Liver Cancer

Guest Expert: Wasif Saif, MD
Associate Professor of Medical Oncology

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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. Wasif Saif. Dr. Saif is an Associate Professor of Medical Oncology at Yale Cancer Center and he is an expert in the treatment and research of liver cancer. Here is Ed Chu.

Chu Why don’t we start off by defining what liver cancer is?

Saif The liver is one of the biggest and largest organs present in our body and there are different functions of the liver. It is basically a cleansing or a sanitation system in your body. In addition, it also produces bile to digest our fatty foods and it also stores glycogen, which is a form of sugar that helps the body to function. Overall, a liver cancer is defined as a primary liver cancer, which is a very important distinction to be made today. When we talk about liver cancer, we are talking about primary liver cancer and that is what we are going to talk about on today’s show, as opposed to a secondary liver cancer. Primary liver cancer is defined as a cancer where the cells are from the liver itself, compared to a secondary liver cancer where the tumor or cancer has spread into the liver from other parts of the body. Liver cancer is defined as the cells of cancer originating from the liver cells.

Chu It is interesting because the liver does appear to be a very common site to which a number of other cancers, such as breast cancer, lung cancer, and colorectal cancer, seem to have a very high affinity for spreading.

Saif Because the liver is the metabolic center of our body and a sanitation factor of our body all the chemicals, toxins, food, everything, ends up in the liver to get purified, detoxified, or to get stored, and I think that is one of the reasons why. The blood supply is really directed towards the liver and most of the cancers end up spreading, and traveling to the liver.

Chu How common is primary liver cancer in the United States?

Saif About 21,750 cases were diagnosed in 2009, but if you look overall in the world about 700,000 liver cancer cases are diagnosed annually worldwide. Although in the USA we may not think it’s a huge problem, worldwide it is one of the biggest problems.

Chu It’s interesting, as you say, in many countries in Asia, China, or Taiwan for instance, liver cancer may actually be the number 1 cancer as compared to in this country.

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Saif That’s exactly true, and that’s one of the important things to know, this is a global disease, that’s the term we use when we talk about liver disease, it’s a global disease, but it’s also very important to know that this is a heterogenous disease. Geographically, this disease seems to have different etiologies, different characters, and different responsive therapies when somebody is diagnosed in Asia compared to Europe, Japan, or the USA.

Chu What age groups are typically affected by this disease?

Saif We most commonly see patients in their late 50s and early 60s with this cancer. It goes by the etiology and the time frame that that etiology or cause needs to develop into cancer.

Chu And what do we know about the potential etiologies, the causes for this disease?

Saif The most common causes can be defined into five groups. The most common is really hepatitis B, hepatitis C, the third common is alcohol abuse, the fourth one is NASH, which is basically obesity leading to fatty liver, leading to cancer, but in addition to that one, there are some inherited causes such as alpha 1-antitrypsin deficiency or Wilson's Disease, and these are the syndromes or diseases where people are developing an inherited abnormality of some enzymes that either lead to fibrosis of the liver, or absence of certain chemicals that are required. In addition, some toxins can also lead to development of liver cancer.

Chu In the United States, what are the most common causes for liver cancer?

Saif Hepatitis C, followed by alcohol abuse, and hepatitis B are the most common, which is very interesting because luckily, we have a hepatitis B vaccination available in the USA, but for some reason Asian countries have more hepatitis B induced liver cancer compared to Europe and USA where hepatitis C seems to be the prevalent mode of causing liver cancer.

Chu There have been some reports suggesting that because of the potential increased incidence of hepatitis C in this country that over the next 10 to 15 years there may be an explosion in the number of patients who develop primary liver cancer.

Saif You are exactly right. There has been a prediction that by 2020 or 2024, around that time, there will be an epidemic of liver cancer induced by hepatitis C. That brings it to attention and brings up the burden on our shoulders that something needs to be done, not only to prevent this cancer by awareness and education, but also to develop some vaccines like the vaccine we have available for hepatitis B.

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Chu: Wasif, can you tell our listeners out there what the common causes, risk factors, are for someone to develop hepatitis C?

Saif: The most common risk factor is, of course, drug abuse, or it can be sexually transmitted.

Chu: Drug abuse meaning intravenous drug abuse?

Saif: Intravenous drug abuse exactly, people getting blood transfusions, or for patients, it can be also sexually transmitted. Definitely these are the three major routes for the development of hepatitis C infection.

Chu: Is there currently a vaccine that can help to prevent the development of hepatitis C?

Saif: Unfortunately there is no current vaccine available for hepatitis C at this time.

Chu: In contrast to hepatitis B?

Saif: Correct.

Chu: It is interesting because I have spent a fair amount of time over the years in Taiwan, and as we talked about in Taiwan and China, hepatitis B has been the number one cause for the development of liver cancer. But, because of very aggressive hepatitis B vaccination, they are already beginning to see a pretty dramatic reduction in the numbers of patients developing liver cancer.

Saif: That’s exactly true, and now luckily, event at the time when my kids were born, we gave them the hepatitis B vaccine. And being in the medical field, particularly dealing with researching blood samples and other tissues, there are certain guidelines by the NCI that doctors, researchers, should be getting vaccinated and should be periodically checked for their titers. Similarly for the general person outside, it is very important for them to know that they need to get vaccinated for their kids, for themselves, for their wives, and for their husbands, because this is a preventable cancer, at least through hepatitis B. However, we still don’t have any vaccine available for hepatitis C except that we should be educating ourselves and tying to prevent the modes which can lead to the spread of this infection.

Chu: Now, is it enough just for someone to have hepatitis B or hepatitis C, or does there have to be underlying liver disease in order for an individual to develop liver cancer?

Saif: Liver cancer is a disease that’s like a cascade of steps. It goes through steps starting from the infection, going to the chronic infection that leads to scarring, then leading to abnormal cell

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development, and finally leading to cancer. Definitely there are a lot of genetic abnormalities that are involved in transforming this abnormal infected liver into cancer and those markers could be P53 or other genetic mutations. These are all involved in that cascade, or the whole pathway, and I think that’s one of the reasons that when you develop infection, it’s a period of 15 to 20 years by the time all those genetic mutations play a role, along with this infection that leads to the development of liver cancer.

Chu So, in most cases, an individual would have already had underlying chronic active hepatitis or cirrhosis in order for them to develop liver cancer?

Saif That’s exactly true, they develop hepatitis B or hepatitis C infection that leads to chronic infection, that leads to cirrhosis which is a scarring of liver tissue that ultimately transforms into liver cancer.

Chu So in general, as you already mentioned, this takes a good amount of time to develop, it isn’t that you have acute hepatitis and then develop liver cancer.

Saif No, I can’t think of it happening that quickly, it definitely takes a longer time and I think that is really the important part to bring home today to our listeners, and that is screening. It brings up the point of how a patient should be screened and who should be screened for liver cancer, especially if they have risk factors such as hepatitis B, hepatitis C, or cirrhosis due to other causes.

Chu On the topic of screening, are there any screening methods? What are the screening methods that can help to detect liver cancer?

Saif There are screening methods available by the American Cancer Society and the American Society of Clinical Oncology, and also the American Gastroenterology Society, which include tests of blood called alpha-fetoprotein, or AFB. Alpha-fetoprotein is a test that is done in the blood, and if this level starts going up that is a harbinger or a risk that somebody is developing liver cancer. In addition to that one, this test is combined with ultrasound, which is done from four to six months to look in the liver to make sure that no abnormal, round shape, nodules are developing in the liver that are concerning for liver cancer. And based on the history of different patients these guidelines are either followed four to six months indefinitely until we follow these patients and make sure that they don’t develop any disease.

Chu What are the typical symptoms that are associated with an underlying liver cancer?

Saif The most common symptom that you see in these patients is fullness, or some kind of pain in the right upper quadrant just below the ribs on the right side. In addition to that, these patients can also feel a lump in the right side of the belly and sometimes these patients can turn yellow, they

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start losing weight, sometimes they see ballooning of their belly and develop fluid there, sometimes they start developing edema and, unfortunately, in severe cases they can also have bleeding in the upper GI tract, or stupor or confusion if they are in the late stages where they have development of so called liver coma.

Chu  If an individual has underlying chronic hepatitis or cirrhosis, will they have these same symptoms, or is this a marked change from their underlying chronic liver disorder?

Saif  It’s comparatively a marked change because it goes through different steps. If somebody is developing cirrhosis, which I mentioned earlier is like a scarring of the liver, those patients can also develop a big spleen and that big spleen, which we called hypersplenism, can also lead to some complications. These patients can also increase the pressure in the portal vein, which is a major vein that brings food from the intestine to the liver and if the blood pressure goes up, which is called portal hypertension, that can lead to a big spleen and can also lead to decreased amounts of platelets, which are the cells in the blood that help prevent bleeding and can also lead to the development of fluid. When we look at liver cancer, I always define it as having two underlying reasons, two symptoms, and two outcomes. One is the underlying liver disease, which is caused by the infection of hepatitis B, hepatitis C, and cirrhosis that can lead to blood being either too thick or too thin. Along with that, portal hypertension and low platelets, and the second symptoms are caused by the cancer, which include weight loss, fever, lumps, and jaundice.

Chu  Should an individual develop any of these symptoms, what should that individual then do?

Saif  They need immediate medical attention. First of all, I really hope and I believe that patients who have these risk factors are being followed up either by their primary doctors or by their gastroenterologist, but if any of these symptoms change or get worse, or they develop a new symptom, to me it’s urgent if not an emergency to see a physician and have further testing done to make sure that this is not a patient who is developing liver cancer, because catching this cancer at an early stage can lead to a potential cure compared to delaying the diagnosis of this cancer.

Chu  And it’s interesting, because certainly at our own institution at Yale Cancer Center, we make a distinction between the gastroenterologist and the liver specialist, what are your thoughts as to who an individual should seek out for medical attention?

Saif  Ideally these patients should be followed by a hepatologist, but I think if a patient with high risk is living in a situation where they don’t have a hepatologist, I think that a gastroenterologist would definitely be a good replacement for those people to follow-up with.

If an individual sees a gastroenterologist, sees a liver specialist, also known as a hepatologist, how is the diagnosis made?

The diagnosis is made in three ways. If we see a rising alpha-fetoprotein, the AFP that I mentioned earlier, if we see a mass on an ultrasound, which sometimes is followed by an MRI or a CAT scan, and sometimes we also look at the biopsy, which is very important. The biopsy is a very interesting topic but it has to be done in the right patient.

Wasif, hold that thought and we will discuss that further on the other side of the break. At this time, we are going to take a short break for medical minute. Please stay tuned to learn more information about the evaluation and treatment of liver cancer with our guest expert Dr. Wasif Saif from Yale Cancer Center.

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. The 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.

Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and Dr. Wasif Saif is joining me this evening to discuss the diagnosis and treatment of liver cancer. Before the break, Wasif, you were talking about the issue of biopsy, maybe for those listeners who may have missed that part, could you tell us a little bit more about your thoughts about who should or should not get biopsied?

Ed, as I mentioned to you earlier, liver biopsies are a very hot topic of discussion, not only in our multidisciplinary liver tumor board, but also many other places. I think it reasonably comes up because the liver is also a part of the body that is involved in clotting factors, and these patients can develop liver cancer which could be close to a blood vessel. So, getting a liver biopsy is a very challenging issue and has to be done by the right people at the right time. At the same time, if we believe that a liver biopsy is too risky in a certain patient, we can also make a diagnosis based on a rising level of a blood test called alpha-fetoprotein with very classic features of cirrhosis on the CAT scan or MRI, or a biopsy of the cirrhosis done in that patient. That’s the reason I brought 16:03 into mp3 file http://www.yalecancercenter.org/podcast/feb2110-cancer-answers-saif.mp3
Chu: Does liver cancer just stay confined within the liver, or can it spread to other parts of the body?

Saif: Liver cancer can spread within the liver. If people have one major lesion and then develop many other lesions in the liver, we call it a satellite lesion. The biggest one is the major cancer and then it can develop into small satellite lesions in the liver, but liver cancer can also develop and spread into many other parts including the lungs, the bones, the brain, and lymph nodes, and even the abdominal cavity. Whenever we decide to move forward with the patient for liver transplant or talking about surgical resection, we at least complete the staging of abdomen, pelvis, and chest and include a bone scan to rule out any presence of bony mass in these patients.

Chu: Wasif, you mentioned that at Yale Cancer Center you have a multidisciplinary team that sees and evaluates patients with liver cancer, again for our listeners out there, could you describe what the different elements of that multidisciplinary team are?

Saif: As we know this is a complex disease and I told you that this is a disease of liver dysfunction and liver cancer. That can give you an insight into who should be involved. For liver disease, we need a hepatologist and/or a gastroenterologist to be involved. These are the people who help us to figure out how to maintain the liver function and if these patients develop any bleeding then we need to have an endoscopy and try to ligate or band those lesions that are bleeding. When it comes to the cancer, it becomes a multimodality field in itself. We need a medical oncologist for patients who are waiting for liver transplant, or for therapy and who are not candidates for liver transplant or surgery. We have a surgical oncologist who is the liver surgeon that takes the tumor out. We have liver transplanters who transplant the liver in a person who is not a candidate for surgical resection. We have intervention radiologists, and these are the people who do certain special procedures such as TACE, RFA, or ethanol injection, and we have radiation oncologists who also are developing TheraSphere, SBIR, or radiation therapy to these patients. In a lump sum, you can see that it is a field about seven to eight modalities including pathology and radiology that should not be forgotten because they are also a part of the team, helping us out to locate the tumor and its metastases as well as to confirm the diagnosis.

Chu: All of the specialists come together to evaluate the same patient who is being seen and then a treatment option is put forward?

Saif: That’s exactly true, not only do we have a weekly tumor board, but we see patients in the clinics and we really try to have direct communication with the physicians, and in addition to that we also have coordinators on the liver team who try to make sure that the information goes from patient to the physician and from physician to the other physicians.

Chu: Again, to review with us when would you consider a surgical approach as being the main treatment option?

Saif: In simple words, if somebody has an isolated tumor in the liver and they don’t have cirrhosis that patient goes to surgery. We definitely know that surgery is the potential cure. So, anybody with no cirrhosis and a lesion which is in the liver with no distant disease, that is a surgical candidate.

Chu: On an earlier show we had Dr. Sukru Emre, who is head of the liver transplant team at Yale, and Dr. Mario Strazzabosco who is a liver specialist, come and talk to us about the role of transplantation. From your perspective Wasif, when would you generally consider, when would your team consider, transplantation as a reasonable treatment option?

Saif: I think for patients who are in reasonable medical condition without any major comorbid conditions, patients who have disease in the liver with cirrhosis that is not resectable, and patients who have tumor in that area without involvement of any major blood vessels, those are the patients that we recommend to see a liver transplanter and then go for liver transplant.

Chu: The issue that we have talked about before with Dr. Emre and Dr. Strazzabosco is the availability of donor livers, is that still an issue?

Saif: That’s still an issue. An average wait time in the United States can range from 18 to 24 months for a patient. Sometimes those patients need our help because if we are worrying about whether their tumor may grow, then we may have to offer them some kind of therapy to at least control the cancer during the interim period while they are waiting to get on the list.

Chu: There certainly have been pretty significant advances in the development of new targeted therapies to treat liver cancer, can you review with us what has happened over the last few years?

Saif: The breakthrough happened about two years ago in liver treatment and the drug, which is approved by the FDA, is called Nexavar, or sorafenib. I encourage the listeners if they are interested to learn more about this drug. There is a great website I found that is very patient friendly, www.nexavar.com. Nexavar is a chemotherapy that is given by mouth, and this chemotherapy helps to prevent the growth of tumor by two modes. It decreases the formation of new blood vessels by the cancer, and at the same time it also inhibits a growth factor called VREF. This...
chemotherapy, when given versus placebo, showed that there was doubling of progression free survival, which means that these patients were alive without tumor growth, and there was also beyond three months survival benefit to those patients who got sorafenib. This convenience part is definitely a major benefit and overall this drug does not overlap any side effects of chemotherapy in terms of having very severe blood counts drop down, or severe nausea and vomiting. So, definitely it is a breakthrough and now it’s the gold standard of treatment for liver cancer.

Chu And there are some newer targeted therapies that are also being developed, is that right?

Saif That’s exactly true Ed. There are a lot of agents under development for liver cancer; erlotinib, or Tarceva, as we mentioned in a previous program for pancreatic cancer, is under development. Sunitinib, which is a drug that was developed at Yale, is also under testing for liver cancer. In addition to that one, many other novel agents are being tested. At the same time, the combination of these two agents and other agents are also under evaluation. We are also trying to think about adding sorafenib with other chemotherapy agents that also have some activity in liver cancer and see if combined together they may lead to a better outcome. We have finished three clinical trials. One was basically a homegrown trial with PHY906, a Chinese herbal medication and we developed that drug in combination with the oral chemotherapy called capecitabine, or so called Xeloda. This combination showed that there was survival benefit in phase 1 and phase 2 clinical trials. We recently published that data and most interestingly we saw that the benefit was much higher in the Asian population with liver cancer compared to non-Asians. In addition to that one, we also worked on a drug called TAC-101, which is a retinoic receptor antagonist, or more like a vitamin A receptor drug, and we also finished a study looking at a drug called S1, and published some data where we found S1, an oral form of 5-FU, given with the enzyme inhibitor shows a survival benefit. The field is still ongoing. I think the most exiting part is that now we can offer something to these patients. Now, the question really arises as to how to use these drugs. Of course it’s very easy to use these drugs on patients who are unresectable and not liver transplant patient. But the question really is how to use these drugs in conjunction with local therapy such as TACE or radiofrequency ablation, and how to use these drugs in patients after transplant or before transplant.

Chu You just mentioned TACE, which is also known as radiofrequency ablation, can you describe for our listeners what that involves?

Saif There are two procedures, among many others, and one is TACE, which is transarterial chemoembolization where an intervention radiologist gives a form of chemotherapy through the hepatic artery into the liver so that it goes to the liver directly and kills the cancer. On the other hand, radiofrequency ablation is a procedure where we pass electrodes either through the skin
or sometimes we pass them by making an incision, and that electrode passes radio waves and by heating the tumor it kills the tumor and destroys the tumor. These two procedures are offered to our patients at Yale Cancer Center as part of multidisciplinary clinic at Yale University School of Medicine.

Chu: There are also some attempts being made to try to basically freeze the tumors, called cryosurgery, what are your thoughts on that approach?

Saif: Cryosurgery is also being done; definitely this has to be done in a certain context to make sure the tumor is away from the blood vessels because it can lead to necrosis or death of cells. That procedure is also given to selected patients at Yale Cancer Center.

Chu: Is there any role for radiation therapy for treating patients with liver cancer?

Saif: There are three roles for radiation therapy in these patients. One is more investigational than under development, which is a targeted radiation therapy at a higher dose, or SBIRT. Our colleagues from radiation oncology are developing those technologies. There is also a role of giving beads of radiation therapy into the liver called TheraSphere, but in addition to that one radiation therapy is also used for palliative reasons. For example, if somebody has pain or bleeding in the liver area, or if somebody developed a disease into the bone or the brain, then those patients are offered palliative radiation therapy to control the cancer and to decrease the symptoms.

Chu: Clearly, for those of us who have been in the field of GI cancers for quite some time now, again liver cancer, for a long time there really weren’t very many active treatments as you say, we have seen some advances. Can you give us a brief evolution of cancer therapy for liver cancer from your perspective and give us your thoughts as to the progress that’s been made?

Saif: I will say that now the shell of the egg is broken, so now we are definitely going to have more and more available to these cases and the good part is that sorafenib is the drug which is now the gold standard for liver cancer, but that’s not the end of the game, that’s just a beginning. That allows us to develop targeted agents knowing that, as you mentioned, there are a lot of genetic mutations and abnormalities that occur though the development of cancer from an infected, cirrhotic liver, to the cancer. Now we are really opening different drugs and we are looking at different drugs and pathways. In addition to that, we have some chemotherapies that have activity in this cancer too such as doxorubicin, capecitabine, thalidomide, gemcitabine, and oxaliplatin, and now we are trying to go back and see if any of these agents, when married to these targeted agents, may work better. The field now is definitely open again and I feel younger now that we can do more for those patients and we have more zeal and zest to improve the outcome for patients with liver cancer.
Chu: Great. As always it has been a pleasure having you on the show and we look forward to having you come back and tell us the progress that’s being made with you and your team in treating liver cancer.

Saif: Thank you very much Ed for inviting me.

Chu: Again I would like to thank Dr. Wasif Saif who has been our guest expert this evening on the treatment and evaluation of liver cancer. Until next week this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

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