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Advances in Liver Cancer

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous 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 1-888-234-4YCC. This week, Dr. Foss and Dr. Wilson are joined by Dr. Stacey Stein and Dr. Tamar Taddei for a conversation about liver cancer. Dr. Stein is Assistant Professor of Medical Oncology and Dr. Taddei is Assistant Professor of Medicine and Digestive Disease at Yale School of Medicine. Here is Francine Foss.

Foss Let's start off by having you give us a brief definition of liver cancer. What is liver cancer, and what kind of patient gets liver cancer?

Taddei Liver cancer is a primary cancer that arises in the liver. There are two major types, one is in the liver cells themselves and that is called hepatocellular carcinoma, the other type is of the biliary cells and that is called cholangiocarcinoma. Primary liver cancer, specifically hepatocellular carcinoma, is actually rising in the United States and there are many risk factors for liver cancers, cirrhosis being by far the most important risk factor for the development of hepatocellular carcinoma. Cholangiocarcinoma can arise in any healthy person, it does not need cirrhosis as a precursor and actually most people with cholangiocarcinoma do not have cirrhosis. The one risk factor for cholangiocarcinoma is a disease of the liver called primary sclerosing cholangitis which is often associated with the later development of cholangiocarcinoma.

Wilson What are some of the symptoms?

Stein Just to take one step back from that question, what is very interesting about liver cancer and is different from most of the other cancers that we treat in medical oncology is that it occurs usually in the setting of longstanding liver disease. So for hepatocellular carcinoma, Dr. Taddei is right that most patients have cirrhosis and that can come from different things such as hepatitis B, hepatitis C, and from chronic alcohol use, and even now from something that we see called NASH cirrhosis which is caused by inflammation from fatty liver over many years and so often these patients have predisposing factors which hopefully have been identified by someone early because for early stage liver cancer, there actually may be no symptoms or the symptoms may be more from their underlying liver disease than the cancer per se. We really rely on are our colleagues out in the community to identify these patients who are at high risk for liver cancer such as those with hepatitis B, hepatitis C, and a longstanding alcohol history, and hopefully they are being screened periodically for early cancer because we have much better outcomes when the cancer is found early.

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- Foss Tamar, you see these patients often times in the liver clinic and you and Stacey have teamed up in at Smilow Cancer Hospital. Can you tell us how you screen patients that you think might be at high risk? And then how do you and Stacey work together to work on those patients?
- Taddei It is very important to underscore what Stacey just said, which is that you have to have an index of suspicion for underlying liver disease. The CDC has just come out with new guidelines that recommend screening for hepatitis C in all people in the United States born between 1945 and 1965, essentially calling the baby boomer generation, also the hep C generation, because this was when hepatitis C was on the greatest rise in the United States. The epidemiology data suggests that the rise in HCC is directly linked to the epidemiological curves in hepatitis C, such that people who were infected in the 1960s have had a latency period and it takes about 20 to 30 years to develop cirrhosis. So sometime around the 1990s, they might have developed cirrhosis, and as that scarring process progresses over time, that is when the risk factor for liver cancer arises. We are seeing a whole generation of people reach their sort of natural history of liver disease such that they are now at risk for the development of liver cancer. So hepatitis B, although we do not see it as much in the United States, it is endemic in other parts of the world and it is very important to compare the epidemiology. In the US, there are between 20,000 to 30,000 new cases of HCC per year, whereas annually there are about 600,000 deaths from HCC around the globe. So there are 350 million people infected with hepatitis B and of those 350 million, between 35 to 87 million will die of hepatocellular carcinoma. So what we see in the US is really the tip of the iceberg. The other major issue in the US is alcoholism leading to cirrhosis and liver cancer and it is important to ask your patients about their alcohol consumption and then, probably the biggest surge in liver disease is related to nonalcoholic fatty liver disease what we call NAFLD in the liver community, and the biggest rise in terms of demographics are in children ages 11 to 19. What is really concerning to us is that that next wave of liver cancer may come in even younger people who have developed fatty liver disease in their childhood, come to cirrhosis in their 20s and 30s, and actually present with liver cancer in their 40s, and that is actually something that we are very concerned about as being the next wave of HCC. Once hepatitis C is actually successfully treated, now that we have drugs that can treat hepatitis C on the order of a 75% cure rate, we are really worried about what the next wave is. All of this has come to pass in the last five years, and we are seeing increasing rates. We have also seen increasing rates in our backyard at Yale-New Haven Hospital, at the Veterans Hospital, and part of the attempt to establish a screening program and detect these patients early is to work across disciplines and to co-localize in clinical settings where we can actually see our patients, deliver a cogent message on what the multidisciplinary plan is and then I can see the patient and Stacey can see the patient, and I can care for their liver disease and she can care of their liver cancer, especially if it is advanced HCC which is really the prevailing role for the oncologist right now, so that helps us to provide very cogent care for the patient.
- Wilson Since there is a connection between hepatitis and hepatocellular carcinoma, some of our listeners may be wondering, what are some of the risk factors for hepatitis?

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- Stein Hepatitis B and C are the two hepatitises that we worry most about. Hepatitis A is usually a self limited infection, so any listener should not worry about hepatitis A. Hepatitis B is an infection that in Asia is often transmitted from mother to child, what we call vertical transmission, and the patients can be asymptomatic for the vast majority of their life and only present later with either cirrhosis or liver cancer. Going back to hepatitis B, if you acquire it in your adulthood, which is more often the case in the United States, for example, it can be acquired from intravenous drug use, from any sharing of bodily fluids, sexual transmission is very common and anybody who is working in the field with blood, for example EMTs or First Responders, have a risk for acquiring hepatitis B. The blood supply in the US is very well screened for hepatitis B, so we see no transmission and have not seen any in decades of this particular virus. Hepatitis C basically was considered to be non A and non B hepatitis until about 1992 when they developed an assay to check for this and were able to identify that this is indeed a different hepatitis, hepatitis C and it is also a blood born pathogen in the sense that you need to somehow or other exchange blood. Now what is very interesting is that although the vast majority of people with hepatitis C have been injection drug users, we also know that there was quite a bit of incident cases during the cocaine era where people were snorting cocaine with straws that were passed from person to person, so even that sort of microscopic contamination in one person's nasal mucosa to another was enough to transmit the virus and 30% of people who have hepatitis C simply cannot figure out how they contracted it. It was in the blood supply until we developed reasonable screening techniques so if people received a blood transfusion prior to 1992 that could be a way that they contracted the virus.
- Foss There is a vaccine that we are giving our kids now and that we have all had against hepatitis B, can you talk about the role of the vaccine in prevention and also whether there is a vaccine or will be a vaccine for hepatitis C?
- Taddei Hepatitis B is a vaccine preventable illness. It is really unfortunate that people still acquire hepatitis B. Everybody in the United States was vaccinated as of 1985, all children received this vaccination during their first year of infancy, and so we have seen a tremendous drop in the incidence cases of hepatitis B, especially in the younger population. In countries like Asia and Africa where they are starting now to do population vaccination we are also seeing tremendously lower rates of contracting the illness. In the United States, again, it is really not that much of an issue expect in sort of endemic areas where you have a lot of immigration, for example. That vaccine is incredibly successful and prevents the illness by giving a protective antibody. The issue with hepatitis C is that it is a very different type of virus, it is not as stable, it has a lot of what we call quasispecies, so it is a smart virus that tends to mutate quite easily and that has provided problems with developing a good vaccine. It was also very difficult to grow in culture, for example, so there have been a lot of scientific hurdles to developing a good vaccine. As far as the future, we are hopeful that there will be a vaccine against hepatitis C, but we are far away from that.

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- Wilson For hepatocellular carcinoma and cholangiocarcinoma, you mentioned the baby boomers, but are there specific age groups that tend to be affected, and is there any gender difference?
- Taddei The age groups that have the highest incidence of HCC in the US are basically that decade around the mid 50s to mid 60s and that actually coincides quite nicely with the baby boomer generation, if you think about it that way. There is absolutely a gender difference; men are much more affected by this disease than women. We are not exactly sure why that is, but definitely more than two to one men to women. There is new data emerging that was actually just discussed at one of our recent conferences that it appears that there might be an uptick in Latin American females with HCC probably related to nonalcoholic steatohepatitis of which the Latino Community is at most risk for based on population genetics probably more than anything else. We do think that over time we will see these demographics and the susceptibilities change with the etiology of the underlying liver disease. I do want to make the comment though that when you are talking about underlying chronic liver disease, as Stacy mentioned, leading to cirrhosis, and then hepatocellular carcinoma, that is a very well established sort of trajectory of some sort of liver injury causing liver scarring, causing more and more avid scarring, and then ultimately leading to cancer that arises in a sick liver, whereas cholangiocarcinoma is a very distinct cancer with a very distinct treatment and we do not really see cholangiocarcinoma that often in cirrhosis. They are very distinct cancers and we keep them extremely separate. In fact, I run a liver tumor board and although we often will present cholangiocarcinoma, I think they are probably better discussed in the GI tumor board where people who have more expertise in dealing with looking at the biliary tree, for example, can entertain those cases.
- Wilson And you mentioned cirrhosis, just so our listeners understand the context that it is related to alcohol consumption, as a general rule, can you make a comment on how much alcohol does someone need to drink to be concerned? Is it okay if they have a glass of wine every couple of days, that kind of thing?
- Stein The guidelines from both the governing bodies of people in gastroenterology and also in internal medicine are that for males you want to have no more than two drinks per day. A drink sometimes needs to be defined very strictly because some of us think of a pitcher when we think of a drink and some of us think of a short glass. The average drink is four ounces of wine, 12 ounces of beer, or 1.5 ounces of spirits, that is what a drink is. So for a man it is no more than two drinks per day and for women it is no more than one drink per day. Having said that, we see a lot of genetic variation in terms of who is susceptible to alcoholic liver disease and who seems to be somewhat immune to it, and we have not teased out scientifically what those genetic differences are, but in patients who come from families with long standing histories of alcoholism and liver disease, those patients should really think carefully about how much they are drinking.
- Wilson We are going to take a break for a medical minute. Please stay tuned to learn more information about liver cancer treatment with Drs. Stein and Taddei.

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*Medical
Minute*

The American Cancer Society estimates that over a thousand patients will be diagnosed with melanoma in Connecticut each year. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key. When detected early, melanoma is easily treated and highly curable and new treatment options and surgical techniques are giving melanoma survivors more help than they have ever had before. Clinical trials are currently underway at Yale Cancer Center, Connecticut's federally designated comprehensive cancer center, to test innovative new treatments for melanoma. The specialized programs of research excellence in skin cancer grant at Yale, also known as the SPORE grant, will help establish national guidelines on modifying behavior and on prevention as well as identification of new drug targets. This has been a medical minute, brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Wilson

Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host Dr. Francine Foss. Today we are joined by Drs. Stein and Taddei and we are discussing liver cancer. Stacey, tell us a little bit about how liver cancer, or cholangiocarcinomas, are diagnosed once you have a suspicion that someone may have one of those problems? Also, tell us a little bit about staging.

Stein

We look at these patients in a multidisciplinary setting. Often the patients have some kind of symptom that prompts imaging, whether it was on surveillance or they had a change in blood work that their liver doctor or primary doctor noticed with a change in their liver function tests, or some kind of symptom, and we can actually make a diagnosis of hepatocellular carcinoma based on imaging alone, which is very unusual compared to other cancers where we always obtain a biopsy and have a tissue diagnosis before initiating any treatment. We also routinely check all these patients at the time of diagnosis for something called an AFP, or alpha-fetoprotein. It is not elevated in all patients with liver cancer, but it is elevated in many and sometimes that just helps cement the picture of the diagnosis that we are making. Patients usually have a CAT scan or an MRI of their abdomen and based on certain features, we can actually see that this looks very characteristic of an HCC. For now, I will focus on HCC because cholangiocarcinoma actually is quite different. To complete that staging, we will also get imaging of their chest and a bone scan, because sometimes liver cancer can travel to the bones. The next thing we do when we think we have a diagnosis of HCC is to complete the staging with that imaging and the reason why that is important is because the staging really determines what the treatment options are for each patient. If a patient has a small tumor that is in the liver, or a couple of small tumors, the first important evaluation is to see if they are a candidate for a liver transplant, or for a surgical resection, and these are two treatments that potentially can offer a cure for a patient. So it is very important that these patients be seen in a multidisciplinary setting, and of course we offer that for all cancer patients at Yale, but I think that liver cancer specifically really highlights the importance of a

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multidisciplinary team. Basically, the patients are at one meeting, being evaluated by transplant, by surgery, by interventional radiology, by radiology, pathology, hepatology, and medical oncology, and we meet weekly to each bring our area of expertise to the diagnosis and discuss treatment options for each patient individually, and I cannot stress enough how important that is to determining what the best treatment options are for each patient. The first determination is to see if someone is a transplant or resection candidate. You asked about staging for patients, and there is something called the AJCC staging, which we use for most cancers, and I have to say that for liver cancer specifically, it is very deficient in giving a picture of how someone with liver cancer is doing and what their treatment options are, and the reason for that is going back to what I said initially, that liver cancers are unique in the way that they occur, usually in the setting of underlying liver disease, and so while the staging system looks at tumor size and where it spread, it does not take into account what someone's liver function is, and this is very important in making treatment decisions for each patient. There are multiple staging systems out there. The reason why there is more than one is because none of them really have turned out to be fully comprehensive that everyone has decided to use. The one that is most commonly used is the Barcelona liver staging system and that does take into account the extent of the HCC, but also the underlying liver function, and so for that it is more useful than the AJCC staging system. There is also a whole other group of treatments that can be available to patients who may not be a candidate for transplant or resection, but they still have disease confined to the liver, and for that, our interventional radiology colleagues are able to do some procedures such as radiofrequency ablation, chemoembolization or radiation using radiolabeled particles such as Y-90. There is a lot of specific decision making that goes into what the best treatment is for each patient and of course as the medical oncologist, I am mostly focused on the chemotherapy or systemic treatment for these patients. There is one FDA approved drug called Sorafenib, or Nexavar, and that is a pill that patients take daily and it has been shown that there is a benefit to patients receiving this drug over placebo. So that is kind of the standard first-line chemotherapy treatment for these patients, but certainly, if someone is a candidate for surgery or other local regional therapies, we usually use those first because while chemotherapy does have a benefit, unfortunately it does not offer a cure.

Foss Can you tell us with the patients who have localized cancers, how often are they cured and how often do they recur?

Stein For the patients that have resection or transplant, we do have cure rates, some of that does depend on the extent of their liver disease, the size of the tumor and also if there is invasion of the tumor cells already in the blood vessels. That is something we often do not know until the time of resection. So the rates of cure can change from 80% for one patient down to maybe only 20%, depending on whether the tumor was already extending into the vasculature, which we see at the time of resection.

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- Wilson Tamar, can you tell us a little bit about the multidisciplinary tumor board. We have mentioned the word multidisciplinary during this conversation, but what are the big advantages for a patient whose case might be discussed in that form as opposed to some other sort of scenarios where that might not exist?
- Taddei Tumor boards have actually been studied in the literature and are actually accredited boards, they are accredited by the American College of Surgeons, and usually by the cancer center that accredits them, wherever that institution may be, in our case at Yale, and they are governed by a series of guidelines in terms of who must be there and how often they must be present. Most tumor boards consist of radiologists, pathologists, and radiation oncologists, and a surgeon, for example, and then tumor boards can be tailored to the specific type of cancer. For example, our tumor board, because there is not a huge role for radiation oncology, we have substituted the interventional radiologist who has a very key role to play in the management of HCC, or hepatocellular carcinoma. You basically go before your cancer committee, which we did about a year ago now, and you ask for them to recognize you as a tumor board and then attendance is taken of all these various disciplines and that attendance should be at least 90% per year. Minutes are derived from these tumor boards, which are suggestions on the care plan and then the tumor registrar can act as a liaison to derive data and statistics based on what we're seeing at our particular institution, and most tumor registrars become certified registrars and then there is a state registrar who compiles data on different cancers at the end of every year, for example. So, there is a lot of oversight, but the role of a tumor board is really multifactorial. Number one, you discuss the case and number two, it is an open forum in the sense that the patient can bring their opinions to the table, but that some consensus should be reached on the plan of care with all of these disciplines at the table, and then that plan of care is implemented, obviously understanding that surprises can happen along the way. These are patients, their cases can change, tumors can grow rapidly, etc., but it is very important to come up with a consensus because there are so many different treatment modalities for liver cancer and so many different disciplines involved. So, even when we say surgery, it is really two surgical disciplines. We have transplant surgery at the table and we have surgical oncology at the table. Both of whom might have very different opinions. For example, once we come to the tumor board with a case, we discuss the case, we discuss that patient's liver function, as Stacey said, because you need to know how healthy the liver is and how much injury it might be able to withstand from a resection, for example. So, these cases are discussed and then we presents the patient with he plan from the tumor board. Again, the literature has shown that tumor boards fulfill two very important roles. They increase the patient's satisfaction and these papers come from both the urology literature and the gynecology literature, patients feel more satisfied when they know that experts have met to discuss their case. Several papers have also shown that many more patients are inclined to enroll in clinical trials if they have been brought before a tumor board, because there is now a new drive to discuss clinical trials at tumor boards and actually tumor registrars collect that data, was the patient discussed in view of the clinical trials available at your institution, for example. So, the one benefit I would like to see

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from tumor boards is the benefit of survival and earlier detection, and I think we probably will show that, at least in the liver world, but we probably need another five or so years to mature that data. Survival takes a while to establish.

Foss Can you talk a little bit about some of the clinical trials they are ongoing at Smilow Cancer Hospital in the area of liver cancer?

Taddei I will talk about one which is a very unique trial looking at the effect of Sorafenib, which is a molecular agent, and this is looking at the effects of Sorafenib on portal pressures and the feeling is that Sorafenib may have some antifibrotic properties, and so this was an investigator initiated trial looking at the patients who have had fully ablated or treated liver cancers to see what the role of this drug is, specifically on portal hypertension.

Dr. Stacey Stein is Associate Professor of Medical Oncology and Dr. Tamar Taddei is Assistant Professor of Medicine and Digestive Diseases at Yale School of Medicine. If you have questions or would like add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.