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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about organ transplant for cancer patients with Dr. Sukru Emre. Dr. Emre is a Professor of Transplant Surgery at Yale School of Medicine, and Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore I do not think that many in our audience including myself think much about organ transplantation and cancer together as a matter of fact, in my field of course, in blood malignancies, we know that some people who have had organ transplants unfortunately sometimes develop certain kinds of lymphomas, very rarely, that we have to worry about, but that is a different story. How does organ transplantation interface with cancer?

Emre Thank you for the question, and I am going to focus on liver only because there are many organ transplants as you know that include heart, lungs, liver, kidney, pancreas, intestine, bone marrow and so on and so forth. And also, recently, we do have composite tissue graft transplant such as extremity transplant, uterus transplant and so on and so forth.

Gore We read about face transplants in the newspaper.

Emre Exactly, the face is another one. But today, I am going to focus on liver transplantation. Transplantation of the liver can be done for many different reasons, and that might be viral diseases such as hepatitis C, hepatitis B, very rarely hepatitis A with acute liver failure, and also alcoholic liver disease and some genetic metabolic liver diseases such as tyrosinemia, urea cycle disorders and so on and so forth.Gore Things which I do not know anything about and our audience do not know anything about either.

Emre But mainly, in adults, we do transplant for hepatitis C and alcoholic liver disease, PSC, PBC, autoimmune liver diseases and any cirrhotic patient can develop cancer.

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Gore I do not think our audience probably knows what a cirrhotic patient is. I mean, I am a little concerned, I am a baby boomer, and I find out that I have hepatitis C, which hopefully I do not, but many people do and they do not know it, so everybody with hepatitis C needs to get a liver transplant? That's pretty scary.

Emre If it is not treated, now thank God, we have new treatments and when

someone gets hepatitis C, development of cirrhosis takes somewhere around 15 years, and before cirrhosis develops, which is what we call cirrhosis – development of scar tissue in the liver. So, when it happens and there is no turning back then patients are going to need a transplant. But if hepatitis C is diagnosed early and treated with the new medications which have 97-100% success rate, then the liver will regenerate itself and transplant will be totally avoided.

Gore So, that is a good advertisement for baby boomers to make sure they have gotten some preventative medical care and if they are in that risk group, get screened for hepatitis that they may not know that they have.

Emre That is correct and the patients that are in the high-risk group are IV drug users and people that get blood transfusions, but most of the time, we do not know how hepatitis C was acquired by the patient. So, therefore, in the high-risk group, we suggest that they should check their hepatitis C serologies. If they are positive, yes there is a treatment.

Gore Gotcha, but when you say, cirrhosis, and you just explained that this is scarring in the liver, you mentioned if I understand it correctly, there are many ways to have that happen outside of hepatitis infections and you mentioned alcoholic liver disease and others, right?

Emre That's right. Hemochromatosis and other ones, and that is why in our specialty as liver doctors, what we call a hepatologist, any patient with liver cirrhosis or scar tissue, that is routine that we will check certain things. One is what we call a tumor marker, alpha fetoprotein and the other one is every 6 months, we do imaging studies, either ultrasonogram or CT scan or MRI just to follow these patients carefully because once scar tissue is formed, scar tissue causes inflammation that may lead to development of cancer, liver cancer –what we call hepatocellular carcinoma.

Gore How often will patients with cirrhosis develop hepatocellular carcinoma?

Emre There are estimates that within 5 years and after diagnosis of let us say hepatitis C, approximately 20% of the patients will develop hepatocellular carcinoma.

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Gore Oh! That is a lot.

Emre It is a lot. And in the United States the number of HCC related deaths is increasing. In 2018, we estimate that approximately 60,000 individuals will develop HCC.

Gore That's liver cancer, right?

Emre Liver cancer, and then among them, approximately 40% will expire just because of HCC-related complications.

Gore And I think, maybe we should just clarify for our listening audience the difference between the kinds of liver cancer that you are speaking about, which arise in the liver and many patients or listeners know people who had tumor in their breast or colon and then develop what they think is liver cancer. Can you explain that?

Emre Correct. And liver cancer or hepatocellular carcinoma is developing from the liver cells. That is what we call primary liver cancer. And there is another category what we call metastatic liver cancers. Someone who had breast cancer or colon cancer or ovarian cancer, the cancer cells then travels through the vessels and nest in the liver, what we call metastatic liver cancer. Which means that the primary of the tumor is somewhere else but it metastasize in the liver.

Gore And if we looked at those cells, they would look usually like the original cells, more like a breast cancer tumor than a liver cancer.

Emre That's right. Let's talk about the pathologic diagnosis. When we have any mass in the liver, we do imaging studies. Sometimes, imaging studies are pretty good to diagnose without biopsy for primary liver cancer. On the other hand, if there is a secondary, we always do the biopsy and when we evaluate the biopsy under the microscope, the biopsy will show us that the primary of the tumor is coming from either the ovary or colon or breast or somewhere else. That will be the way that we can diagnose it.

Gore For the purpose of this conversation, we are mostly restricted to the kinds that arise in the liver, is that right?

Emre That's right. Today, we are going to strictly talk about primary liver cancer.

Gore I see. And those other cancers, it does not really matter if the liver has scar tissue or not, right? The liver is just like a sponge that can soak up these cells.

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Emre Correct. And we do not need to have the cirrhosis or scarring of the liver to develop other metastatic cancers.

Gore Okay, thank you for that clarification. Now, you mentioned that people who have cirrhosis or scarring of the liver are followed by liver specialists hopefully and they do some blood tests on a regular basis and scans on a regular basis to detect early tumors if possible right?

Emre That's right. So, early diagnosis is really important and that is the aim for scrutinizing the patient, that we will know if a small tumor is developing. If we capture the tumor early, for sure the treatment is going to be easier, and we have different treatment modalities, which we will talk about.

Gore And I would imagine, and tell me if I am wrong please, that if you are

screening people every 6 months, the tumor cannot get so big in 6 months, am I wrong about that?

Emre Most of the time you are right, but sometimes we have surprises as well and then sometimes tumors grow very fast and I just want to make sure that everyone understands, the balance between the tumor and the host body is something amazing. Sometimes, it works in favor of the body or patient and sometimes it works in favor of tumor and the tumor may grow very fast. But you are right, most of the time that tumor growth is not going to be very fast if we follow them carefully.

Gore What happens if say, I am one of these people who have cirrhosis unfortunately and I am being monitored diligently and leading a good life and they detect a tumor and they suspect that it may be liver cancer, what happens next?

Emre Well, depending on the tumor location, depending on the tumor size and also depending on how sick the patient with liver scarring is, because liver scarring or liver cirrhosis will cause a lot of damage in the body.

Gore Medical problems?

Emre That's right. Many medical problems and that includes development of fluid in the abdomen, losing muscles and the patients will become jaundiced and their eyes become yellow, that is what we call jaundice and they may have some itching, pruritus and they lose their muscle mass and their coagulation or blood clotting is not going to be normal and they may develop many infections. Therefore, depending on how sick the patient is related to the liver cirrhosis and depending on the tumor location and size, we may craft many different treatment modalities and we can use many different modalities.

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Gore Let's start with a relatively fit person if that exists in this category.

Emre It is possible the patient may have what we call compensated liver cirrhosis, which means that someone who is working fulltime and a good energy level, but liver is cirrhotic.

Gore If I saw them on the street, I would not think they are sick?

Emre Exactly, you are right on that. Those patients, if we capture the tumor early, then the option is depending on the location of the tumor, we may resect the tumor, surgically remove the tumor or we can use what we call ablation techniques, which we have many different forms of them. Sometimes, what we call radiofrequency or microwave ablation.

Gore Microwave? You put them in an oven.

Emre No, we don't, but what it is basically is that we have, under the ultrasound guidance, our interventional radiologist stick a needle in the middle of the tumor

and then generate with microwave and because of the tip of the needle will become really hot with the microwave and then with that or radiofrequency ablation does the same thing, and the aim is just to cook the tumor.

Gore Cook the tumor?

Emre The tumor becomes totally dead. That is what we call microwave ablation or radiofrequency ablation. And another technique an interventional radiologist will use is they will stick a needle in one of the groin arteries that travels with small catheters.

Gore Similar to what you do with the heart cath?

Emre That's right. Similar to a heart cath. They travel through the vessels into the liver, get close to the tumor and first they give a high dose of chemotherapy directly in the tumor and then they knock down the vessels, arteries feeding the tumor. Once the tumor loses all arterial supply, then the tumor will become necrotic. This is another way of handling the tumor, what we call transarterial chemoembolization or TACE.

Gore Wow, this is really fascinating and I want to talk more about that after the break. But right now, we are going to take a short break for a medical minute.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest Dr. Sukru Emre and we are discussing organ transplant for cancer patients. Sukru, before the break you were telling a fascinating story of patients who have an isolated liver cancer tumor in their cirrhotic liver but they are pretty healthy and you told us you can cook the tumor with microwaves, which sounded kind of gross to me, but I will take your word for it, and then you mentioned that a radiologist can put a catheter in

and choke off their blood supply, that does not sound super-pleasant either, are those effective therapies?

Emre Yes they are. We use those therapies as a bridge to transplantation many times, and if patients are healthy and if a tumor is removable, we also prefer to do liver resections. Resections mean removing the diseased part of the liver together with tumor with margins, with normal healthy liver tissue around it. Healthy meaning that there is no tumor involvement. So, clear margins. That is also a good treatment for patients with HCC, hepatocellular carcinoma, or liver cancer I must say. Recently, we started doing this operation using a laparoscopic technique, what we call robotic surgery that we do not need to make a large incision, that we work with small ports and work inside via these ports and remove the tumor and then with a small incision we take the tumor out of the body. That will allow us to keep the patients less in the hospital and they do not need to deal with large incisions and the infection related to that and so on and so forth. That is a cool technique.

Gore Yeah, not exactly like gallbladder surgery, I am sure it is more complicated?

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Emre The surgery is surgery, and I cannot say that any surgery is easy having done this job for the last 35 years. Sometimes, we start the case and it is easy and it will become a disaster. Sometimes, you think that is going to be difficult, but it will go very nicely and smoothly. So, surgery is surgery. We will inform our patients before surgery all the complications and other things, but I believe that honesty is the best policy and I personally, and my colleagues as well, we do not want to sugar coat anything and the patient and family should know all the complications, side effects and the problems with the surgery. Pros, cons and everything. We discuss, we do not need to scare them but we will give them the right information.

Gore Of course, I wonder since they come in with a scarred liver in the first place and now you are taking it out, I do not know a third of the liver or half the liver, how much do you take out?

Emre If there is scar tissue in the liver and we are limited to remove which part of the tumor, we have certain tests. I do not want to get into details, but if the tumor is central, that will require removing a large part of the liver. We may prefer to use ablation techniques, then we list the patient for transplantation and the ultimate goal is do transplant for those patients. But if the tumor's location is suitable for resection, towards the edges and only located to one lobe of the liver, then we will be able to perform the resection. Still, resection is the gold standard for the treatment of the cancer.

Gore I see. And the rest of the liver is good enough to take over?

Emre Well, we have certain calculations as I said. We measure the liver volume with imaging techniques and then we calculate the volume we are going to

remove and then we have certain calculations whether the remnant liver, the part we are going to leave with the patient will be enough to cope with the metabolic needs of the patient or not. If that is the case, we prefer to do resection. If it is not, we go with the ablation technique, and when we go the ablation techniques, the ultimate goal is going to be transplant the patient.

Gore Why do these patients who have had these ablation techniques still need a transplant? Is it because of the underlying cirrhosis or because there is a chance you still haven't killed all the tumor cells?

Emre The ablation technique and the technology is getting better, but recurrence can occur. Recurrence may occur in the ablation cavity or around that or sometimes since the liver is tumorogenic, which means that liver has scar tissue everywhere, other tumors can pop up in other places.

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Gore Not related to liver?

Emre Not related to the first one necessarily. Therefore, the ultimate goal to cirrhotic patients will be the transplant.

Gore I see, but it is not so easy to get a liver donated right? I mean, there is a waiting list?

Emre There is, yes. Anyone who meets the criteria to be listed, we list, and there is a national organization, what we call UNOS. UNOS stands for United Network for Organ Sharing. That is the governing body of all organ transplants in the United States, it is the contractor to HHS, a federal government agency basically. So, once we list the patients, the patients should wait on the list. There is a standard allocation algorithm for liver transplantation. In adults, what we call MELD, Model End-Stage Liver Disease scoring system based on the patients and their liver function tests, everyone will get a score and that score, the lowest is the 6 and highest is the 40. Based on that, they are listed. Then they wait on the list until a suitable organ becomes available. On the other hand, as you mentioned, finding an organ is very difficult. Organ shortage is very acute. There is a big gap between supply and demand of these organs, therefore, every year approximately 20% of the listed patients expire while they are waiting because of the organ shortage. Society, transplant society, we did a lot of development to alleviate organ shortage, that what we use and standard criteria organs and also we do use living donor liver transplantation.

Gore Can I ask you about that?

Emre Which is a good way to alleviate the organ shortage.

Gore And can that be done even in this case of these patients with liver cancer? Can you use the partial liver transplant?

Emre Exactly, we can. Indeed, in the early days of living donor liver transplantation, most of our patients were patients with liver cancer actually. Because as you mentioned and that I actually echoed the same thing, sometimes patients are healthy and liver functions are perfectly fine, their MELD score is going to be very low. On the other hand, if there is a tumor in the liver growing causing trouble, then they may not get the organ as timely. This was in the past, and that is why we did more living donor liver transplantation for cancer patients, but now with the new organ allocation algorithm in cancer patients, as long as their tumor is under control, they may be eligible to get extra MELD points.

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Gore Because they have cancer?

Emre Since they have a cancer, yes.

Gore And on these partial living donor transplants, are the donors in general people from the family?

Emre Not necessarily. We do Good Samaritan donors. We do friends and the neighbors and altruistic donors, and we use many different types of donors. The most important thing for us is that this is the gift of life, it should come from the bottom of the donor's heart, and buying or selling organs is a federal crime. There should not be any foul play. As long as the people are genuine and people they want to donate, we are okay to use them as donors. I must say that donor evaluation is very tedious. What I call it, the donor evaluation is the best possible checkup anyone ever can get.

Gore Yeah.

Emre There are many tests, there are many exams and cardiac evaluations, imaging studies, head to toe and everything else. Then, we do many calculations and the part that we are going to take from the donor should be enough for the recipient. The liver part we are going to leave with the donor should be enough for the donor's initial functions. The liver is what we call a blessed organ or privileged organ. The reason why is the liver grows back. So, if you take the head of the liver, the liver grows back to normal size in approximately 6 weeks to 8 weeks timeframe.

Gore No kidding, that's fascinating.

Emre It is a fascinating thing indeed and this has been known since ancient Greek if you remember Zeus punishing Prometheus spewing the fire and he was changed to rock and every morning, an eagle comes and eats the liver and during the night, the liver regenerates and grows back, and it goes on and on. So, since then, we do know liver is a privileged organ that grows back. It takes approximately 6 weeks to 8 weeks. It is not that fast that I mentioned in the mythology. On the other hand, it takes 6-8 weeks' timeframe and grows

back. Based on the studies we have done as well as the others, the growth of the liver is somewhere around 98% to 103%.

Gore Wow! That's fascinating, and it still seems like a tremendous act of altruism to do this because you mentioned all the intensive medical investigations that need to be performed, but I imagine the surgery is not pleasant either for the donor.27:39 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-1125-Podcast-Emre_346777_5_v1.mp3

Emre Well, for the donor, they are going to have pain, they are going to have an incision. We plan to do the donor operation robotically so that they can have less incision and better outcome and less pain for sure. When it comes to donor evaluation, we do not want to have any stone unturned that we can kick ourselves later on, that is the complete evaluation and explanation of all the complications and other things, and donors are heroes. Despite the fact that they are going to have and they are going to have possible complications, they want to do this thing, and that is why they are heroes and we do everything to make them better during the case and after the case as well. Our commitment to donors is forever. We do see them yearly for follow-up and as long as they come. But most of time they say 2-3 years later, I am fine Dr. Emre.

Gore And are ready to donate again.

Emre Of course they cannot, but I wish that they would come for yearly visits every time, but sometimes we have a hard time to convince them to come for yearly checkups. By the way, I want to say one more thing, when they donate, they do not need to pay any single cent for this operation. Everything is covered by the recipient insurance.

Gore I see. I had an agenda of many more things to talk about but believe it or not, we are out of time. It has been great having you on Yale Cancer Answers. It has been a terrific show about liver cancer and we will have you back shortly because we have a lot of fascinating things to talk about.

Emre Thank you and I want to say one last thing, that after transplant, if tumor is in the liver, if that is treated previously with resection or the ablation techniques, after transplant, the patient's outcome is excellent.

Dr. Sukru Emre is a Professor of Transplant Surgery at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.