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Hepatocellular Carcinoma: Clinical Priorities from Detection to Liver Transplantation

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Medical Breakthroughs from Penn Medicine

Advancing Medicine Through Precision Diagnostics and Novel Therapies

Liver Transplantation for Hepatocellular Carcinoma

Narrator:

Welcome to **Medical Breakthroughs** from Penn Medicine: Advancing Medicine Through Precision Diagnostics and Novel Therapies.

Dr. Mennen:

I am your host, Dr. Barry Mennen, and with me today is Dr. Maarouf Hoteit, who is the Director of the Multidisciplinary Liver Tumor Clinic at the Hospital of the University of Pennsylvania and the Program Director of the Transplant Hepatology Fellowship and Assistant Professor of Medicine at the Perelman School of Medicine. Today we will be discussing liver transplantation for hepatocellular carcinoma.

Dr. Hoteit, welcome to the program.

Dr. Hoteit:

Thank you, Dr. Mennen. Thank you for the invitation, my pleasure to contribute here.

Dr. Mennen:

We're happy to have you. For the first question, I'd like to know, could you tell us some of the characteristics of hepatocellular carcinoma and who is at risk for it?

Dr. Hoteit:

Hepatocellular carcinoma is cancer that arises from liver cells. As many of the audience already knows, it is a cancer that tends to happen in the vast majority of the cases in the background of chronic liver disease, especially liver cirrhosis. Patients with cirrhosis of any cause, be it due to hepatitis C, hepatitis B, fatty liver, alcohol or other causes of liver disease, would have this inflammatory reaction within the liver and extensive scar deposition. We believe that this is the process that puts some of the liver cells at risk of transforming into malignant cells of hepatocellular carcinoma. It is a peculiar cancer in that it often occurs in the background of inflammation and

scarring in the organ that we, as physicians, can identify as a problem. And while we, as physicians, evaluating a patient are able to identify that this particular patient is at risk of liver cancer and be able to act on it, the difficulty is that this process is often asymptomatic, so patients really have no symptoms to alert them to this risk, and this is why it is so important to identify patients who are at risk of liver disease to test for possible etiologies of liver disease and treat the etiology of the liver disease when possible. And the best example there is hepatitis C, which is usually completely silent, for which there are recent developments of highly successful and tolerable treatment options. The main challenge in this situation is to identify patients who are at risk for hepatitis C and have no symptoms.

So, historically, we test for hepatitis C in patients who have currently abnormal liver tests or patients who have had risk factors such as prior drug use or a blood transfusion before 1992, and more recently, it has been shown that screening anyone who has been born between 1945 and 1965 is cost effective because the vast majority of people who are infected with hepatitis C in the US are born between these two dates. The idea is that if you're able to identify the risk factor for hepatocellular carcinoma, act on it, then there is a possibility of preventing the disease, or at least have the opportunity to detect it early.

Dr. Mennen:

Yes, getting liver enzymes at routine physicals is a big help, I would understand.

Dr. Hoteit:

Correct, absolutely. And then there are, in addition, even in patients who have normal liver enzymes, there is a recommendation to screen anybody who's born between 1945 and 1965.

Dr. Mennen:

Right, in that high-risk group, absolutely. Now, how common is hepatocellular carcinoma in the US?

Dr. Hoteit:

Over the past few years, hepatocellular carcinoma has consistently featured in the top 10 causes of cancer death in the United States, and the disturbing trend is that consistently over the past couple decades, the incidence of primary liver cancer, which is predominantly represented by hepatocellular carcinoma, has been constantly increasing, and it has risen to be the most rapidly increasing cause of cancer death in men. It is the most rapidly increasing in terms of the rate of increase in incidence, and we believe that this is mainly related to this increased number of patients with hepatitis C who have had the infection for more than two decades at this point in time and are, therefore, at higher risk of cirrhosis and subsequent liver cancer.

Another problem that is looming around the corner is the obesity epidemic in the United States, and obviously, it is associated with increased risk of diabetes, which is a risk factor for hepatocellular carcinoma, and increased risk of nonalcoholic steatohepatitis and subsequent cirrhosis, which represent cancer risks as well.

Dr. Mennen:

Yes, that was going to be my next question, actually, because we see that in practice now and we didn't use to. What is the usual timeframe for patients with nonalcoholic fatty liver to develop cirrhosis if left untreated as far as not changing diet, etc.?

Dr. Hoteit:

It is highly variable. We know that patients with fatty liver may develop cirrhosis. The majority don't. What would be very helpful in assessing these patients is to find out the time when they are diagnosed how likely are they to have steatohepatitis as opposed to simple fatty liver and how likely are they to have fibrosis of the liver. In the absence of significant fibrosis, we think most of these

patients do very well. As to what is the best technology to figure that out, there is a bit of controversy there. There's no question that you can get the best data out of a liver biopsy; however, this is the most invasive thing you can do in this situation. And there are some noninvasive tests that are imperfect that are increasingly used. And so the point is to figure out how much fibrosis and how much scar tissue is associated with fatty liver, and that's going to determine how concerned we are going to be about this problem.

Dr. Mennen:

Is there a way to reduce the risk of hepatocellular carcinoma and detect it at a curable stage, aside from the points that you've already made, of course?

Dr. Hoteit:

Treatment of the underlying liver disease before cirrhosis develops is known to reduce or even eliminate the risk of liver cancer. In hepatitis C and hepatitis B, this has been clearly shown. Once cirrhosis is present, while treatment of the underlying disease may reduce the risk, the risk of cancer appears to be persistent even if hepatitis C is eliminated once cirrhosis is established. So, anyone who has cirrhosis of any cause should undergo active surveillance for HCC every 6 months, and the best way to do screening or surveillance based on the current data is to do an ultrasound of the liver every 6 months. The role of adding alpha fetoprotein testing to ultrasound is more controversial. The problem with alpha fetoprotein is predominantly the fact that it's a good marker for advanced disease; it's not a great marker for early disease, the stage at which you want to diagnose it. And so, we definitely need better blood tests and better biomarkers for early hepatocellular carcinoma. This isn't an area of active research at this point in time, but what's available to us in the clinic at this point in time is essentially ultrasound every 6 months is the best thing we have for now.

We know that it is very important to detect hepatocellular carcinoma at an early stage. The symptomatic stage, if you do not do any screening tests and await symptoms before you make a diagnosis of hepatocellular carcinoma, it is often at an incurable stage. Usually, these are large HCC tumors for which we really don't have as many options that could cure it.

Dr. Mennen:

What are the treatment options for hepatocellular carcinoma at the various stages and according to the histopathology?

Dr. Hoteit:

As you know, the treatment of hepatocellular carcinoma is complicated by the fact that in over 90% of the cases you have a background of a diseased liver. The liver has cirrhosis and you have cancer in it, so one has to consider not only status of the tumor, as you do in most cancers as well as the overall health of the patient in determining what treatment you choose, but you have an additional disease that's coupled with the cancer, which is the impairment in liver function. It plays significantly into what treatment you end up choosing. So, if the patient is in good health and the liver function is intact and there is no portal hypertension, which is a common complication of cirrhosis, and the tumor is limited in the liver to an anatomically resectable location, surgical resection tends to be the treatment of choice and it may be curative.

There are instances where even a less invasive procedure could be curative. When a particularly small tumor, typically less than 3 centimeters or so, is sitting in a particularly favorable location in the liver, it could be treated percutaneously with an ablation catheter. So, this is the technique of percutaneous ablation which could be curative as well, and in several case series tends to result in a cure rate that is comparable to surgery in small tumors.

The difficulty with hepatocellular carcinoma, however, is that it has this propensity to spread very early from one point in the liver to another. It has a tendency to invade the local vessels surrounding the tumor and use that as a pathway to allow tumor cells to migrate from one area in the liver to another, and this is why, whether it's with resection or with ablation, the recurrence rate of hepatocellular carcinoma after these treatments is relatively high.

Transplant, on the other hand, is a curative option in some select cases where resection is not possible because of impaired liver function or because of the tumor already having shown signs of spreading within the liver. And in cases where resection, transplant and ablation are not possible because of the extent of the tumor, while the tumor is still limited to the liver, you can deliver liver-directed therapy. There are several modalities that can be used that use the fact that hepatocellular carcinoma is a tumor that gets the vast majority of its blood supply from the hepatic artery, unlike the remainder of the liver that gets predominantly portal venous blood. And so, you can use the hepatic artery feeding the tumor as a pathway to deliver treatment, either chemotherapy directly into the tumor or radiation-emitting beads and radioembolization. And more recently, external radiation has been used to treat tumors limited to the liver when other modalities are not possible.

And, finally, if the tumor has had the chance to spread outside the liver, then there's only one standard therapy in this scenario, which is a drug called sorafenib. It's an oral antiproliferative drug for hepatocellular carcinoma. But in this scenario, we also often encourage patients to consider clinical trials as there are a few clinical trials with new, promising agents for patients who have more advanced disease.

Dr. Mennen:

If you are just tuning in, you are listening to Medical Breakthroughs from Penn Medicine on ReachMD. I am your host, Dr. Barry Mennen, and I am speaking with Dr. Maarouf Hoteit, Director of the Multidisciplinary Liver Tumor Clinic at the Hospital of the University of Pennsylvania.

Now, Dr. Hoteit, who is a good candidate for liver transplant to treat hepatocellular carcinoma?

Dr. Hoteit:

As mentioned, transplant is a curative option in some cases where the tumor is limited to the liver. One has to see that there is no invasion of the liver vessels. One has to consider a situation where surgical resection is not possible, either because it is too risky to remove part of the liver in the setting of liver dysfunction or because the tumor has already shown signs that it's spreading from one point in the liver to another.

The important issue in considering a liver transplant as a treatment for hepatocellular carcinoma is that if the tumor burden appears to be extensive within the liver even as there is no evident cancer outside the liver, we know in this scenario based on early experience with liver transplant for hepatocellular carcinoma that transplant tends not to cure the cancer, and that would entail a high chance of cancer recurrence after transplant with devastating consequences -- obviously, having a patient undergo a major procedure like transplant and still have cancer.

So there have been criteria that are set to limit the amount of tumor within the liver that transplant can reliably cure. These standard criteria put a cap on the size of HCC that can be treated with transplant, and the standard numbers are for a single lesion. If somebody has a single tumor, it can be as large as 5 centimeters. And a patient may have 2 or 3 lesions in the liver as long as the largest lesion is no larger than 3 centimeters. This is what defines the Milan criteria, which had been developed in the late 1990s and are considered the gold standard for transplant for hepatocellular carcinoma. The idea is that if you allow the tumor to be much larger than that, then the recurrence rate makes transplant a risky endeavor. However, since then we, and others, have tried to expand on these criteria to allow more patients access to a potentially curative transplant, and there are instances where the tumor does exceed the Milan criteria; however, we do not see evidence of tumor outside the liver and the vessels of the liver are not invaded by the tumor. And we tried to deliver some of the modalities that I mentioned earlier, chemoembolization, radioembolization or external radiation, to see if we are able to shrink the tumors to a size that fits the standard criteria, and this is a process called downstaging, and we have been using these techniques increasingly to allow access to transplant to an increasing number of patients with hepatocellular carcinoma.

Dr. Mennen:

Could you say a few words also about concomitant diseases? Are there some that take the patient out of the realm of transplant consideration, whether it be diabetes or kidney disease or COPD?

Dr. Hoteit:

Certainly, the liver transplant evaluation involves not only considering the primary indication for transplant, which in the case of our discussion here is hepatocellular carcinoma, but the transplant evaluation involves a multidisciplinary team including transplant surgeons, hepatologists, nurse coordinators, nutritionists, social workers, cardiologists and other specialists depending on the specific patient situation, whose main role is to be able to identify that the patient is capable of undergoing a major surgical procedure like a liver transplant with good, long-term outcomes. In general, factors such as having diabetes or having COPD would not in and of themselves and as a single factor exclude somebody from being considered for transplant. There are factors that are taken into consideration, and we evidently have to be careful in diabetics that they don't have significant coronary artery disease that would interfere with their ability to undergo a major surgical procedure, but there is really only a few conditions that maybe would be very problematic in terms of considering a transplant off the bat without an extensive evaluation. Things like having had a recent cancer with a high risk of recurrence, say somebody who has lung cancer or lymphoma or something of the sort that may interfere with our capacity to give them immunosuppression later on could be a problem, but there are many other conditions that may interfere with our capacity to do transplant that require a multidisciplinary evaluation followed by a committee review of the situation to see if we're able to get the patient through a transplant procedure.

Dr. Mennen:

The concept of listing the patient after evaluation?

Dr. Hoteit:

Essentially, the process goes with the patient being evaluated by the different specialists for the candidacy for basically being able to undergo the procedure and having a good long-term outcome, and the next step would be a liver transplant selection meeting. That is a meeting that is set up with the specialists who evaluated the patient where a case is discussed and sort of opinions are shared, and the committee has a whole makes a decision as to whether or not we think that this patient is able to undergo a transplant safely. And once that happens, the patient becomes on the liver transplant waiting list. The reason for the need for a waiting list is the fact that there aren't enough donors for transplant to provide everybody who needs a liver transplant with an organ as soon as they are listed, so the waiting list is a creature of that necessity to have prioritization of who should get the next transplant. And patients with liver cancer do get increased priority for transplant because of their liver cancer. However, their waiting time, while variable in different parts of the country, and especially because of new rules that are recently implemented, tends to be at least 6 months. The waiting time for transplant in hepatocellular carcinoma can be as long as a year to a year and a half, but at the minimum it's 6 months. And one of the issues to deal with, obviously, in this situation is that you're having somebody with cancer in the liver and you don't want that cancer to progress or grow during their waiting time. Often times what we end up doing is using treatment modalities such as chemoembolization, radioembolization or external radiation to try and control tumor growth while patients are waiting for their transplant.

Dr. Mennen:

Now, is liver donor transplant an option to treat hepatocellular carcinoma?

Dr. Hoteit:

You mean living donor transplant? And I think it is in general an excellent option for treating patients with liver cancer. So, a living donor is typically a family member or a friend of the patient who is in great health and they match the patient's blood type and they're able to donate part of their liver. It ends up helping the patient tremendously by taking away the issue of waiting. Often times what happens in this situation is as soon as the donor is evaluated and they are determined to be somebody who is able to undergo the donation procedure safely, a transplant can be scheduled and the patient does not have to wait for their turn on the liver transplant

waiting list. In that sense it is an advantage. It is a procedure that is more technically challenging for the surgeons, so you want to be in a center that has a lot of expertise in this particular procedure. There are a few centers in the country that excel in this. I happen to be lucky to be in one of them. And so it is an excellent option, and it does save the patient for having to wait too long for their transplant.

Dr. Mennen:

What is the long-term outcome of patients treated with liver transplant for hepatocellular carcinoma?

Dr. Hoteit:

Of course, any patient who gets a transplant needs close monitoring long-term to ensure that the transplanted liver functions well and to monitor for any side effects from the immunosuppressive drugs that we use in this scenario to prevent organ rejection. Having said that, liver transplant is associated with the highest cure rate of HCC of any treatment modality. Between 80 to 90% of patients who get a transplant for HCC are cured and have an excellent long-term survival. The reason for that and for this high cure rate is that on one hand, with transplant, unlike with other treatment modalities, you do remove the entire organ. We know this tumor has this capacity to send cells to other parts of the liver very early on, and because the entire liver is removed, it tends to be more likely to remove the entire tumor burden, as opposed to a limited resection where there may be invisible tumor cells in the rest of the liver that have developed before the surgery is done. The other main advantage is that you are removing a diseased organ that has cirrhosis in it and replacing it with a healthy liver from a donor, so you're able to also prevent complications related to liver dysfunction in the same process, as such one of the treatments for solid organ cancers that has the highest cure rate in this group of patients.

Dr. Mennen:

Dr. Hoteit, thank you for being with us today and sharing your insights.

Dr. Hoteit:

Thank you so much. It's a real pleasure.

Dr. Mennen:

I am your host, Dr. Barry Mennen. Thank you for listening to this program on liver transplantation for hepatocellular carcinoma.

Narrator:

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