MANISH SHARMA: Hello. My name is Manish Sharma. I'm from the University of Chicago Medicine. Today I'll be talking with you about Hepatocellular Carcinoma and our multidisciplinary approach to this disease.

First, for my disclosures, I will first not have any potential conflicts of interest regarding this topic, but I will be discussing therapeutic uses that would be considered off-label.

The learning objectives of the talk today are to describe risk factors and diagnostic criteria for HCC, to describe prognostic factors and staging of HCC, to understand the indications for various therapies, including surgical, local-regional, and systemic therapies, and to describe barriers to the successful management of this disease.

First, HCC is a global disease. As you can see from the graph here, the global burden of the disease far exceeds that which we have in the United States. In fact, in the United States, only 3.7% of cancer deaths are due to this disease, while globally over 9% are. The five-year survival rate in the United States of 16% is likely greater than it is globally.

If you look at the incidence of HCC by sex and world area, two things jump out. First, the disease is more common in men than in women throughout the world. And second, the most common areas where the disease is most prevalent are in Asia and Africa at the top of this graph.

This corresponds to the risk factors for the disease. One major risk factor for HCC is hepatitis B. And this map shows the prevalence of hepatitis B surface antigen throughout the world. As you can see, the dark green areas are where the prevalence is highest, and those are in Southeast Asia, sub-Saharan Africa, Greenland, and parts of South America, and northern Canada.

As you can see from this map, for hepatitis C, which is another major risk factor for HCC, the most common areas of prevalence are in Northern Africa, and as well as areas of Asia and the remaining part of Africa and Australia.

The risk factors for the disease are summarized here and can be divided into two major categories, common risk factors and rare risk factors. Common risk factors include the hepatitis B carrier state, which is the number one cause of the disease globally, and which can happen with or without cirrhosis of the liver preceding it.

Chronic hepatitis C infection is the number one cause in US and Europe in the West. And other major common causes are alcohol and non-alcoholic fatty liver disease, which is a growing cause of the disease.

Rare causes include hereditary causes, such as hemochromatosis, alpha-1 antitrypsin deficiency, and dietary causes that are common in certain parts of the world but relatively rare overall.

Screening recommendations for HCC amount to ultrasound every six months. And it's cost-effective to do screening if the risk of HCC is greater than 1.5% per year in patients with hepatitis C or 0.2% per year in patients with hepatitis B. The way I interpret these rules are that patients who have hepatitis C and cirrhosis should be screened, whereas all patients with hepatitis B should be screened.

Here's a diagnostic algorithm for HCC. If a liver nodule is detected on ultrasound, it should be managed according to size. If that nodule is less than 1 centimeter in size, the ultrasound should be repeated three months later. And if it's growing or changing in character, it may need to be investigated further. If it's stable, repeat ultrasound can be continued.

If the nodule is greater than 1 centimeter in size, an imaging test should be performed, either a multiple-phase CT scan or an MRI. If on these imaging tests the arterial hypervascularity and delayed venous washout is present, then the diagnosis can be made, and HCC is the diagnosis.

Otherwise, if it's not detected, the other imaging modality should be attempted. And again, if the classic radiographic findings are observed, then the diagnosis of HCC can be made. If neither imaging modality can make the diagnosis by radiographic criteria, then a tissue biopsy may be necessary to make a diagnosis.

AFP has been studied greatly as a diagnostic test in this disease. AFP is Alpha Fetoprotein. This can be detected in the serum. However, there are limitations to how useful the test is. Various cut-offs have been looked at as far as their sensitivity and specificity for making the diagnosis.

And here we have the Receiver Operating Characteristic curve, or ROC curve, of serum AFP to try to distinguish patients who have HCC from those who do not. As you can see from the graph, cut-offs such as 16 nanograms per milliliter or 20 nanograms per milliliter would have relatively decent sensitivity at 60%, but not perfect specificity.

Whereas higher cut-offs, such as 100, 200, or 400 nanograms per milliliter, would have excellent specificity, but sensitivity goes way down at these higher cut-off thresholds. As a result, AFP has not entered into the diagnostic algorithm that I showed on the previous slide.

Prognostic factors for HCC include four major ones. First, the severity of the underlying liver disease is very important as this is a competing cause of mortality in patients with HCC. Secondly, tumor size and number, where larger tumors and larger numbers of tumors portend a worse prognosis.

Third is vascular invasion of, typically, the hepatic vein or portal vein. And fourth is extra hepatic metastases, disease in the liver-- outside the liver, I mean, in the lungs or brain or bones.

The Child-Pugh score is a way of categorizing the severity of underlying liver disease in patients with cirrhosis and has been around since the 1970s. The criteria for calculating the Child-Pugh score include total serum bilirubin, serum albumin, INR, and the presence of ascites or encephalopathy.

Patients who have Child class A have the least severe cirrhosis with 5 or 6 points on the score. Whereas patients with Child class C have the greatest degree of cirrhosis with points in the 10 to 15 range.

And as you can see here, the Child-Pugh score does also predict for life expectancy and perioperative mortality related to cirrhosis. But for the purposes of patients with HCC, patients who have more severe underlying liver disease have a worse prognosis from their cancer as well.

The Barcelona Clinic Liver Cancer staging classification, or BCLC classification, was designed to help understand the severity of HCC. And it goes with stage 0, stages A through C, and stage D. Stage 0 patients are those with very early stage disease who are typically going to be candidates for curative intent therapies.

Those with stages A through C are patients with a single nodule or multiple nodules. And depending on their performance status, are classified as A, B, or C. Stage D patients are those with poor functional status, or Child-Pugh C disease. And those are considered end-stage patients who are typically not candidates for anticancer therapy.

The treatment options for HCC are multidisciplinary as highlighted here. First, surgical options include hepatic resection or orthotopic liver transplantation. Local-regional therapies include Radiofrequency Ablation, or RFA, Transarterial Chemoembolization, or TACE, and Transarterial Radioembolization, or TARE. Systemic therapies include only one that is FDA-approved, sorafenib, and a number of investigational agents that are currently being studied.

The indications for hepatic resection in an ideal candidate include a solitary tumor with no evidence of vascular invasion, no evidence of portal hypertension, and well-preserved liver function, i.e. Child-Pugh A. Most surgeons also prefer to operate on patients with tumors less than or equal to 5 centimeters in size, although this is not a hard and fast rule.

As far as outcomes from hepatic resection, there is a small risk of mortality within the first 30 days after surgery of around 5% in this study. And overall survival at three years is roughly 55%, and at five years roughly 37%, with disease-free survival as shown here. It should be noted that the majority of patients included in this particular study were Child-Pugh A.

There are some controversies regarding hepatic resection, in particular precise criteria for resection. Should we be doing surgery on larger tumors? Or should we be doing surgery on patients who have Child-Pugh B cirrhosis? There's also the question of whether adjuvant therapy after resection is helpful.

The indications for transplant are well-defined by the Milan criteria, which have been adopted by UNOS and counterparts in other parts of the world for allocating organs for transplantation. The criteria are a single tumor less than or equal to 5 centimeters in size, or up to three tumors, each of which are less than 3 centimeters in size. There can be no evidence of vascular invasion, and there should be no evidence of extrahepatic metastases, whether lymph nodes or distant metastases in other organs.

Outcomes from transplantation include a significant upfront mortality of about 5% at 30 days and about 13% at three months. Overall survival numbers are a little bit better than those for hepatic resection, with a three-year survival around 70% and five-year survival around 62% in this particular study. The majority of patients, it should be noted, were Child-Pugh B and fit the Milan criteria in those who were studied here.

A number of controversies exist regarding transplant as well. First, the typical median waiting period for patients on the transplant list is greater than six months, and many patients that come to their disease, either their cancer or their underlying liver disease, prior to that. There's also not enough data on living-donor transplants, which are becoming more and more commonly done.

And new adjuvant therapy is a question mark while awaiting transplant. Many patients are sent to medical oncologists with the hope of undergoing some form of therapy to try to delay the progression of the disease, but it has not been studied and proven to be the case that this can be done successfully. Options might include local-regional therapy or systemic therapy in such cases.

In terms of comparing hepatic resection and transplant, comparative observations are that these are actually somewhat different patients. Most of the time, hepatic resections are done on patients with Child-Pugh A disease, while transplant is done on patients which Child-Pugh B disease.

There's higher perioperative mortality with transplant, but lower three-year and five-year overall survival with hepatic resection, mainly due to disease recurrence in the remaining liver. The bottom line is to really know which of these is better, we would need a randomized trial comparing them, and that's something that is not likely to be undertaken any time soon.

Local-regional therapies, as I mentioned before, include three major types, radiofrequency ablation, transarterial chemoembolization, and transarterial radioembolization. Radiofrequency ablation, or RFA, involves giving thermal energy to a lesion, or burning it, in order to cause tissue necrosis.

Transarterial chemoembolization and transarterial radioembolization are both conducted in a similar manner and at this institution are done by interventional radiologists. In TACE, or Transarterial Chemoembolization, it can be done conventionally using chemotherapy, typically doxorubicin or cisplatin in an emulsion, or with drug-eluting beads, typically doxorubicin. Transarterial radioembolization is typically done with yttrium-90 microspheres, which are made out of glass or resin.

The approach for transarterial therapies is shown here, whether we're talking about TACE or TARE. The interventional radiologist makes a small puncture into the femoral artery down here in the groin and uses a catheter to make their way up into the aorta and into the hepatic artery.

There they shoot some dye and identify which arteries are feeding the tumors most directly, and by doing so can administer chemotherapy beads, or the yttrium-90 microspheres in the case of TARE, directly into that artery to be able to block blood supply to the tumor, as well as treat it with the chemotherapy or with the radiation locally.

The indications for local-regional therapies are patients who are not a candidate for curative resection or transplant, or if there is an anticipated long wait on the transplant list, those who have no evidence of extrahepatic disease, and those with well-preserved liver function, typically Child-Pugh A or B, and adequate performance status, typically ECOG 0, 1, or 2.

The procedure, whether it's TACE or TARE or some combination of the two, can be repeated any number of times in an individual patient, oftentimes on the order of several months of time elapse between each successive procedure.

RFA was studied extensively in the 1990s and early 2000s and was found to be superior to the prior standard of care, which was percutaneous ethanol injection. In this study, patients with Child-Pugh A and B disease and tumor size less than 3 to 4 centimeters were looked at. And this is a meta-analysis of four separate, randomized, control trials that compared three-year overall survival between RFA and percutaneous ethanol injection.

As you can see here from the summary plot, in all four of these clinical trials RFA was found to be superior to percutaneous ethanol injection. And if you combine all the data from the 652 patients together, the odds ratio was approximately 0.5 in favor RFA.

TACE has also been extensively studied. And in this particular meta-analysis, they were looking at patients with Child-Pugh A or B cirrhosis and tumors that were greater than 3 centimeters in size and/or multinodular, many different sites of disease. A number of different studies were conducted, and seven of them were summarized here for a total of 480 patients.

Again, if you combine the data from all 480 of these patients, the odds ratio favored TACE compared to the control, in this case, again, percutaneous ethanol ejection, with an odds ratio of 0.54.

There is some rate of adverse events with TACE. But as you can see here, the mean rate was approximately 6%, which was certainly acceptable given the advantage that it conferred.

TACE and RFA have also been looked at as a combined therapy, where a patient typically would receive their chemoembolization on the first day, spend the night in the hospital, and then receive the radiofrequency ablation to the same exact lesion the second day.

In a large, randomized control trial conducted in China, 291 patients were studied in this manner and had tumor sizes between 3 and 7 and 1/2 centimeters in size. They all had Child-Pugh A or B cirrhosis.

As you can see from the Kaplan-Meier plots here, TACE and RFA combined outperformed either TACE alone or RFA alone in the entire population. And when you broke it down by uninodular HCC versus multinodular HCC, on the right side of the screen here on the top, you can see that in uninodular HCC, TACE-RFA outperformed RFA. And in multinodular HCC, TACE-RFA outperformed TACE alone.

In terms of whether to use TARE or TACE in any individual patient, this is an area of ongoing controversy. In a retrospective study conducted down the street from us at Northwestern with 245 patients, abdominal pain and increased ALT and AST were more common with TACE.

But there were no significant differences between the two groups with respect to overall survival. And the time to progression was longer with TARE than with TACE, 13.3 months versus 8.4 months, although it's unclear of the significance of that given no differences in overall survival. At the end, I think this study showed that either of these options are probably equally good, and the decision may need to be made on a patient-by-patient basis.

This algorithm shows a summary of local-regional therapies available for treatment of HCC. On the left side of the algorithm, you can see that radiofrequency ablation is the preferred modality for patients with Child-Pugh A or B cirrhosis and single tumors that are relatively small, or three nodules that are all very small, less than 3 centimeters in size. If the lesions happen to be in an area that's difficult to approach with RFA, there still may be a role for percutaneous ethanol injection.

For patients who have disease that is multinodular or with a large, solitary lesion greater than 5 centimeters in size, these patients should probably be approached with either TACE or TARE. Those who have portal vein thrombosis, or portal vein invasion, or who have larger tumors are more likely to benefit from TARE as compared with TACE.

The only FDA-approved systemic therapy for HCC is sorafenib. The approval for this drug was based on two large clinical trials, one of them conducted in Europe and one conducted in the Asia-Pacific region. Sorafenib is a multi-targeted, oral, small molecule, tyrosine-kinase inhibitor. These two phase III double-blind trials were conducted in patients with Child-Pugh A cirrhosis and who all had BCLC stage C disease, or advanced HCC.

In Europe, the study showed that median overall survival with sorafenib was 10.7 months compared to 7.9 months with placebo with a hazard ratio of 0.69 and the Kaplan-Meier curve as shown here on the left side of the screen. In the Asia-Pacific region, the median overall survival with sorafenib was 6.5 months compared to 4.2 months with placebo with a hazard ratio of 0.68 and a Kaplan-Meier curve as shown on the right side of the screen here.

Both studies showed very similar benefits for sorafenib compared with placebo, although the absolute overall survival numbers were quite different between the two groups. A number of different reasons for this difference had been postulated, and ultimately most investigators believe that the difference here is due to the biology of HCC being different in the Asia-Pacific region than in Europe.

Oftentimes the risk factors underlying the disease are different, with hepatitis B being more common in Asia-Pacific region. Regardless, the results of these two studies combined showed that sorafenib was superior to placebo in treating the disease and lead to drug approval.

It's important for both investigators, physicians, and patients to know the common toxicities of sorafenib in patients with HCC. I took this chart from the drug label that's approved by the FDA and is in the prescribing information for the drug. As you can see here from the chart, the most common toxicities with sorafenib that were not present in the placebo group were diarrhea, weight loss, hand-foot skin reaction, alopecia, and hypertension.

I also included fatigue on the chart just to show that although fatigue is a very commonly reported symptom in patients receiving sorafenib, it was also commonly observed in patients treated with placebo, reflecting the fact that fatigue may just be an underlying symptom of the disease rather than a drug effect.

In patients who do experience toxicity from the drug, it's important to know the dose modifications that can be made in order to improve tolerability and allow patients to remain on the drug. The starting dose of sorafenib is 400 milligrams twice daily. And typically, the first dose reduction would be to reduce that to 400 milligrams once daily or 200 milligrams twice daily.

Since the drug comes in 200-milligram tablets, it's oftentimes easier to simply reduce from two tablets in the morning and two tablets at night to one in the morning and one at night. For a second dose reduction, it could be either 400 milligrams by mouth every other day or 200 milligrams daily.

It's also very important to know how sorafenib is handled in patients with liver dysfunction since patients with HCC, many of them have underlying liver disease and abnormal bilirubins at baseline. In a study conducted by the CALGB, it was shown that since sorafenib is primarily metabolized in the liver by CYP3A4, dose adjustments do need to be made for patients with underlying liver disease.

They divided patients into different dosing cohorts based on the severity of their liver disease and explored what maximum tolerated dose could be found in each of those cohorts. I highlighted here that patients who have a bilirubin greater than three times the upper limit of normal, but less than 10 times the upper limit of normal, could not even tolerate 200 milligrams every third day of the drug. And these are patients that, in my clinical practice, I do not even attempt to treat with the drug due to tolerability issues.

This algorithm shows summary treatment recommendations for HCC incorporating both liver-directed therapies, surgery, and systemic therapy, sorafenib. As you can see here, this all is based on the BCLC staging classification with stage 0 on the left side of the algorithm and stage D patients on the right side of the algorithm.

On the left side, with stage 0 patients, curative treatments such as resection or liver transplantation or RFA can be attempted as outlined here. For stages A through C patients, some of these patients may be candidates for curative-intent therapies such as RFA, especially the stage A patients. However, stage B or C patients should be treated with local-regional therapies such as TACE or TARE or with systemic therapy such as sorafenib.

And the way I make this decision is typically based on size of tumors and number of tumors. Patients with more tumors and larger tumors typically are going to be ones that are going to respond better to systemic therapy. Whereas patients with smaller tumors typically will undergo a local-regional therapy such as TACE or TARE, especially if they have only a single tumor.

It's important to recognize that TACE, TARE, and sorafenib are all considered palliative therapies, meaning that they are not expected to cure the disease but simply to slow down disease progression and by doing so, hopefully prolong life with good quality of life.

For stage D patients way on the right side of the screen here, these patients are considered very advanced and could not tolerate local-regional therapy or sorafenib. So really should be treated only with symptomatic management and really are candidates for Hospice care.

A number of barriers to the management of HCC exist. The first is lack of early detection and underlying liver disease, which together create a very small window of opportunity for therapy in this disease.

Many patients who arrive at my clinic are already too ill to undergo therapy of any kind, whether it be local-regional therapy or systemic therapy. So early detection and recognition of underlying liver disease as a time-limiting factor are a key to make sure that patients are treated in a prompt manner.

There's also clinical and biologic heterogeneity with this disease, which is, of course, a common theme in every solid tumor, but really make it challenging in that certain patients may respond to a therapy because the biology of their tumor allows that therapy to work, whereas others do not.

There's also a lack of prospective randomized studies to establish clear standards of care in this disease. I mentioned resection versus transplant has never been studied head-to-head and may never be studied because of the fact that surgeons have specific preferences about their approach to these patients.

TACE versus TARE have never been studied directly head-to-head. And TACE versus TACE plus sorafenib had never been studied head-to-head in a study that has completed accrual. There is an ongoing study right now that will hopefully answer that question of whether local-regional therapy plus systemic therapy is better than local-regional therapy alone.

There also is a lack of systemic therapies that are more effective than sorafenib at treating this disease. A number of systemic therapies have been studied in the last several years and compared to sorafenib in phase III trials. And unfortunately, all of them have failed to establish a new standard of care that's better than sorafenib.

As you can see here, median survival in the two arms for all these randomized trials were not significantly different, except in the case of sunitinib versus sorafenib, in which case sorafenib was superior to sunitinib. The different drugs that were studied were brivanib, sunitinib, linifanib, and erlotinib in combination with sorafenib.

Unfortunately, since all these trials were negative at establishing a new standard of care, sorafenib remains the only FDA-approved option in this disease and the only true standard of care for systemic therapy.

A number of other therapies for HCC are being studied currently in phase III trials. And I've highlighted here major categories of drugs and therapies that are being studied just to show how active this area of research really is. All of us in the field are very hopeful that at least one or two winners will emerge from this large group of therapies being studied so that we can continue to move the needle and improve survival in this disease.

I want to highlight that clinical practice guidelines are available, and a number of them were used in helping to create my talk. The American Association for the Study of Liver Diseases and the European Society for Medical Oncology both have guidelines for the practice of HCC on their websites.

And I want to thank you for your attention and mention that questions, comments, or referrals can be sent to me at the following email address.