OVERVIEW

Hepatocellular carcinoma (HCC) prevalence is currently increasing and is a major source of morbidity and mortality in the US and around the world. Management of HCC requires multidisciplinary collaboration across several specialties, with hepatologists and oncologists fulfilling key roles within the care team. Dr. Amit Singal provides learners with a comprehensive review of HCC, beginning with the epidemiology and burden of disease and taking learners through optimal systemic management. Dr. Signal will provide practical guidance related to the use of tyrosine kinase inhibitors, VEGF inhibitors, and immunotherapy in patients with HCC, including guideline recommendations, adverse event management, and the role of combination therapy.

CONTENT AREAS

- HCC epidemiology and prevalence
- Morbidity and mortality of HCC
- HCC screening recommendations and tools
- Current and evolving HCC staging systems
- HCC treatment paradigms
- Systemic therapies for HCC: mechanisms of action, efficacy, and safety
- Inequities in HCC diagnosis and management
- The role of the multidisciplinary team in HCC care

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Discuss the potential clinical impact of ongoing clinical trials evaluating novel therapies for patients with advanced HCC
- Assess the current and emerging first- and second-line systemic therapy for patients with advanced HCC
- Create personalized treatment plans that take into account HCC and underlying liver disease pathogenesis and incorporate screening and multidisciplinary care
- Develop individualized treatment strategies for patients with advanced HCC, including optimal management of adverse events/immune-related adverse events on the background of underlying liver disease

FACULTY

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TARGET AUDIENCE

This activity was developed for national audience of heptalogists, as well as medical and radiation oncologists, interventional radiologists, and hepatic surgeons.

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Amit G. Singal, MD, MS

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The estimated time to complete the activity is 1.25 hours.

This activity was released on March 18, 2021 and is eligible for credit through March 18, 2022

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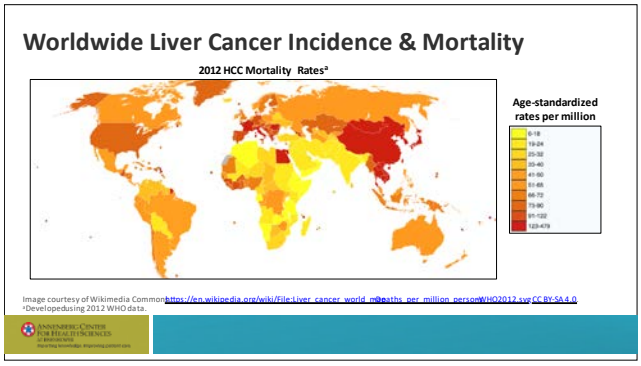
Annenberg Center for Health Sciences

RED LINE: OVERVIEW

Editor's Note: This is a transcript of a webcast presented in February 2021. It has been edited and condensed for clarity.

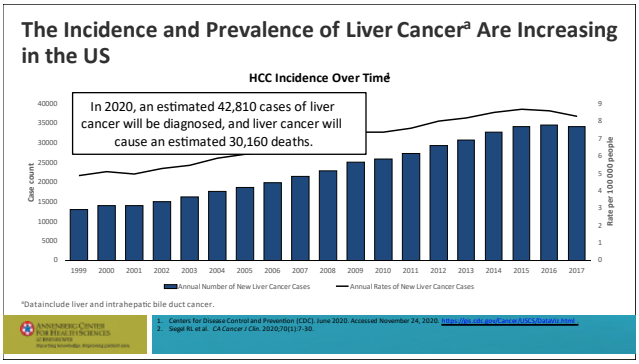
Current Epidemiology & Future Trends

When we think about liver cancer, this really is a global problem. As you can see here, we see that liver cancer impacts every country across the world. We see the highest incidence and mortality rates in East Asia and in Africa, driven by high rates of endemic hepatitis B in those areas.



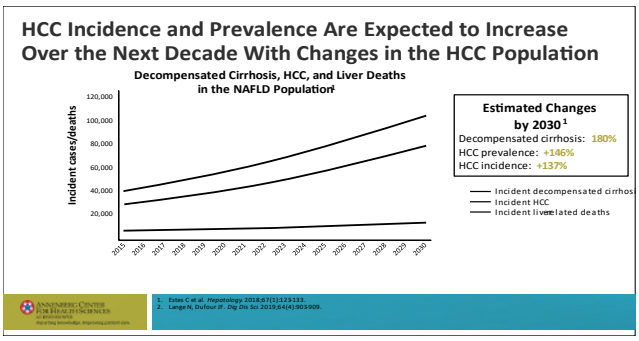
Overall, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death. Now, in the United States, we see an intermediate incidence and mortality rate, but one of the things that's become increasingly clear is that the incidence and prevalence of liver cancer are rapidly increasing. In 2020, there's going to be an estimated 42,000 cases of liver cancer that will be diagnosed, and about 30,000 liver cancer-related deaths.

There's a couple of things that you can note on this slide. The first is the nice and steady increase in the trend for the number of liver cancer cases, and the second is the ratio for incidence and mortality. And one of the things that really is noteworthy is that many of the new cases of liver cancer really translate into that number of deaths, highlighting the very poor survival for liver cancer as a whole.

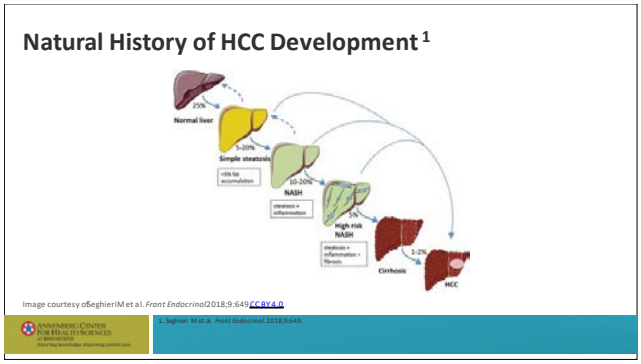


We've seen what's happened over the last several years, and one of the things that we note is that the incidence of liver cancer is expected to continue increasing over the next decade, given changes in our at-risk patient population. When we think of our at-risk patient population, there's many risk factors that go into this, with cirrhosis being the strongest risk factor. As we've seen progress in some of those risk factors such as hepatitis C, hepatitis B, we have a growing cohort of patients with nonalcoholic fatty liver disease as well as alcohol-associated liver disease. And these increasing conditions continue to create a cohort that's at high risk for HCC.

As you can see from this modeling study, the number of HCC cases in the United States, as well as worldwide, is expected to continue increasing over the next decade. In fact, over the next decade, the number of nonalcoholic fatty liver disease-related HCC cases is expected to increase over 100% in the US.

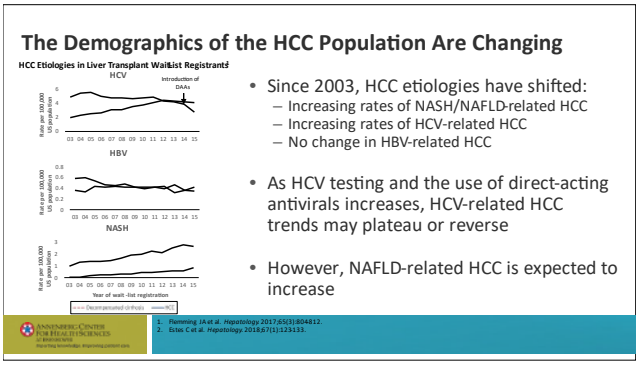


On this slide, we can see the natural history of HHC development. This is something that I've already referenced, that the primary at-risk cohort for HCC in the United States really is patients with underlying chronic liver disease, if not cirrhosis at the time of diagnosis. Most people start their life with a normal liver, and what we have, over time, is that people can develop chronic hepatitis. This can be related to many different conditions, whether that's viral hepatitis or, as you can see in this case, nonalcoholic steatohepatitis. You have this chronic liver injury which progresses to fibrosis, and at some point, to cirrhosis. And once a patient has cirrhosis from any one of these etiologies, that patient has an annual risk of developing HCC somewhere between 1% and 4%, a truly high-risk state. And it's at this point when somebody has cirrhosis that we say that that patient is high enough risk where they warrant undergoing routine screening.



Now when we take a look at the demographics, we've seen many shifts over time. Once again, something that I've referenced over the last couple of slides. We've seen improvements in our antiviral treatments, most notably the introduction of the direct acting antivirals, in which we've seen dramatic decreases in our hepatitis C patient population, as well as notable reductions in risk of HCC among patients with hepatitis C-related cirrhosis.

However, over the same time period, we've seen an increase in patients with nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis, the state where you have ongoing inflammation and fibrosis. This really relates to many more Americans, and many people worldwide, having obesity, diabetes, and what we see is that nonalcoholic steatohepatitis is really the liver manifestation of this metabolic syndrome. We've seen an increasing number of patients with NASH and, as I referenced in that prior modeling study, we anticipate also seeing an increasing number of NASH-related HCC over the next decade.

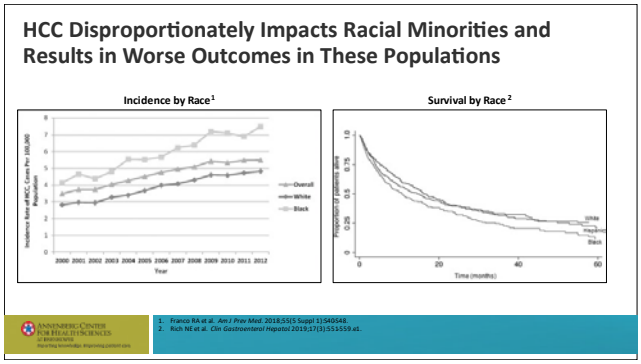


When we take a look at other demographic features in terms of distribution of HCC, one of the strongest risk factors for HCC is that we know that this really disproportionately affects men. Up to 4 in 5 cases of HCC occur in men. This is related to many different reasons, variable distribution of at-risk factors. We know that men typically have worse behaviors in life, higher obesity, higher diabetes, higher smoking, higher alcohol use. And so many of these behavioral risk factors translate into a higher HCC incidence and prevalence. In parallel, we know that there's hormonal differences, higher testosterone, lower estrogen in men, and these hormonal differences also likely influence the higher HCC incidence in men related to women.

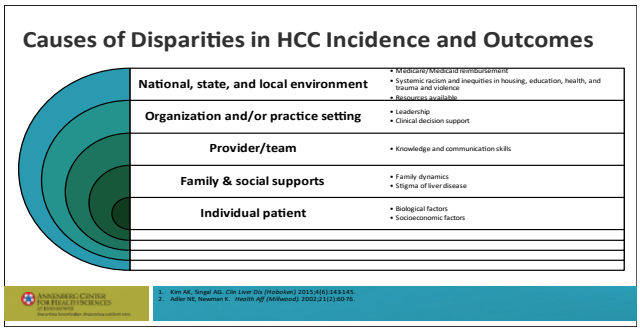
The other demographic that we see that's strongly associated with HCC in the United States is that HCC disproportionately impacts racial, ethnic minorities and low socioeconomic status communities. And so we see higher incidence in these communities, as well

as worse outcomes. And this was nicely highlighted by a couple of studies.

As you can see here, when you take a look at the incidence rates for HCC by race, we see higher incidence rates among African Americans, as well as Hispanics, compared to non-Hispanic whites. When you take a look at prognosis, you also see racial, ethnic disparities by race ethnicity. This really is something that has gained a lot of attention, once again recently, and something that's really an intervention target as we move forward.



When we think of the causes of disparities in both HCC incidence and outcomes, we understand that this is really related to multilevel factors, including differences at the individual level, the provider and family community level, as well as the system and community level. And so to counteract and reverse these disparities, we're going to need interventions that really act upon all of these different levels if we really want to move from a model of health disparity to health equity in the near future.

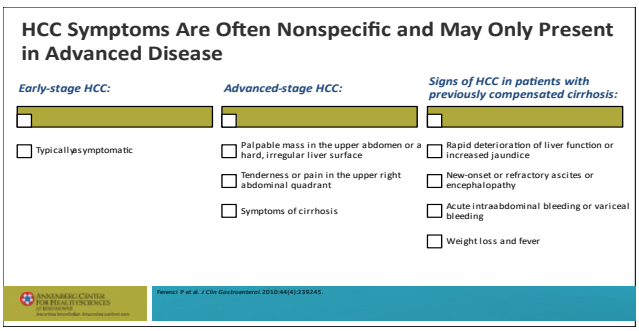


Screening

One of the key things that we have to remember is that HCC is asymptomatic at an early stage, and typically, when people present symptomatically, this really means that the tumor is quite large and will not be amenable to curative therapies in the vast majority of those cases. So it's critical that we find these before patients present symptomatically.

The other thing that's worth noting here on this slide is that these symptoms that people can present with in terms of advanced stage HCC are often nonspecific. When you have a patient with cirrhosis where there is this high-risk state and patients present with any of these nonspecific symptoms, it is important for us to have a high level of suspicion and to perform a diagnostic evaluation at that time.

Some of those symptoms in which people can present include typical cancer-related symptoms, such as pain related to capsule stretch, they can present with weight loss, they can present with worsening hepatic function. And so, if you see any of these symptoms in a patient with cirrhosis, I do think it's important for us, once again, to pursue diagnostic evaluation and to rule out the presence of HCC. But once again, I would argue that the goal is to find people at an early stage when we can facilitate curative therapies, and once again, this is when patients are typically asymptomatic, highlighting the importance of screening. This is really why many of the professional societies have recommended that we do routine screening in at-risk individuals.



Here, in this table, we can see many of the at-risk individuals in which screening is recommended. Now, when we look at this, this can be quite simplified when we think about this in terms of implementation in clinical practice.

The first, the top of the slide, is really subgroups of hepatitis B. So when you take a look at this and we take a look at patients with vertical transmission, ie, when patients acquire this at or near the time of birth. We talked about this in the beginning section of epidemiology, that the highest burden of HCC happens in East Asia driven by high rates of endemic hepatitis B in those areas where there's high rates of vertical transmission. And so when we think of this, this is really vertical transmission, ie, Asian male, Asian female, hepatitis B carriers. And this is greater than age 40 or age 50. And the reason why it's younger in Asian men compared to Asian females is because once again we talked about males being higher risk. So we start that screening at an earlier age because these people are at higher risk of developing HCC at an earlier age.

The other group that you can see here, African or North African blacks with hepatitis B, and these patients are also very high-risk and we start screening at an earlier age. We see family history of HCC, once again a risk factor. So this is another risk group for hepatitis B which warrants screening outside of cirrhosis.

Now, beyond these first 4 rows, you take a look at everything below there in terms of the established risk factors for screening, and all of these are cirrhosis patient populations, whether that's viral hepatitis, other risk factors, this all can be compressed into cirrhosis from any etiology. And like we talked about early, this is where that risk of HCC is somewhere on the order of 1% to 4% per year, ie, a high risk state in which screening is cost effective.

Therefore, HCC Screening Is Recommended for High-Risk Populations

There is no universal definition of high risk; factors to consider include patient age, health status, function, and willingness and/or ability to adhere to a screening program

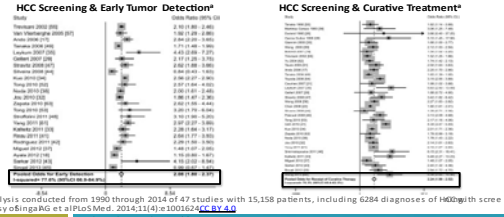
Benefit	Population Group	Threshold incidence for screening efficacy	Incidence of HCC
Established	Asian male HBV carriers ≥40 years	0.2	0.4%-0.6% per year
	Asian female HBV carriers ≥50 years	0.2	0.4%-0.6% per year
	HBV carrier with family history of HCC	0.2	Higher than without family history
	African and/or North American Blacks with HBV	0.2	Occurs at a younger age
	HBV carriers with cirrhosis	0.2-1.5	3%-8% per year
	HCV cirrhosis	1.5	3%-5% per year
	Stage 4 PBC	1.5	3%-5% per year
	Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
	Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
	Other cirrhosis	1.5	Unknown
Uncertain	HBV carriers <40 years (males) or <50 years (females)	0.2	<0.2% per year
	HCV and stage 3 fibrosis	1.5	<1.5% per year
	NAFLD without cirrhosis	1.5	<1.5% per year

1. Marrero JA et al. *Hepatology* 2018;68(2):723-750.
2. Kanwal F, Singal AG. *Gastroenterology* 2019;157(1):54-64.

There are no randomized control trials for screening in cirrhosis patient populations. There was a randomized control trial that was attempted in an Australian patient population years ago, but that trial had to be terminated given insufficient enrollment because most of those patients wanted to be screened. Even though we don't have randomized data, we do have several cohort studies that establish a strong association between screening and improved outcomes, whether those outcomes are early tumor detection, curative treatment received, or improved survival.

Here you can see from a meta-analysis that we conducted now about 7 years ago, when you perform screening you see significant improvements in early detection as well as curative treatment received. Now in this meta-analysis, we also looked at the pooled odds of surviving 3 years and we also found, once again, a strong association with improved survival with the implementation of screening. Even though we don't have randomized data, I think that these cohort studies really highlight that screening is associated with improved outcomes.

Implementation of HCC Screening Programs Can Improve Outcomes



[a]In a meta-analysis conducted from 1990 through 2014 of 47 studies with 15,158 patients, including 6284 diagnoses of HCC, with scree

Singal AG et al. *PLoS Med.* 2014;11(4):e1001624.

In contrast to the lack of randomized data in patients with cirrhosis, there was a large, randomized control trial in patients with hepatitis B. This randomized control trial was conducted over 15 years ago in China and randomized over 18,000 people to receive screening or no screening. Once again, a chronic hepatitis B patient population.

As you can see from this table, those patients who were in the screening group who developed HCC had significantly better outcomes than those patients who were found to have HCC in the control group. We see significant improvements in early detection, we see significant improvements in terms of curative treatment received, and notable improvements in terms of survival. And most notably, this is the highest quality data that really shows that HCC screening is associated with reduced HCC mortality.

In a Randomized Controlled Trial, Screening Was Associated With Earlier Tumor Detection and Improved Survival[a]

	Screening group (n = 86)	Control group (n = 67)
Stage		
Stage I	61%	0
Stage II	14%	37%
Stage III	26%	63%
Small HCC	45%	0
Treatment		
Resection	47%	8%
TACE/PEI	33%	42%
Conservative treatment	21%	51%
Survival (%)		
1-year	66%	31%
2-year	60%	7%
3-year	53%	7%
4-year	53%	0
5-year	46%	0

[a]In a randomized controlled trial of 18,816 patients aged 35 to 59 years with HBV infection or a history of chronic hepatitis in Shanghai.

Zhang BH et al. *J Cancer Res Clin Oncol.* 2004;130:417-422.

When I take a look at these data overall—randomized control trials in hepatitis B, several cohort studies in cirrhosis patient populations—really highlight the strong data that support our implementation of HCC screening in routine clinical practice.

Now, unfortunately, despite the strong data showing associations with improved outcomes, we know that HCC screening is unfortunately underutilized in clinical practice. So once again, this is a systematic review and meta-analysis that we published just this past year, taking a look at all of the studies that have looked at how often HCC screening is used in clinical practice. And, overall, we found that HCC screening was utilized in less than 1 in 4 patients with cirrhosis.

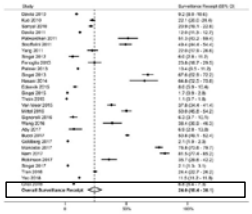
When we take a look at the subgroups, we find higher rates of HCC surveillance in those patients being followed by subspecialists than those patients being followed by primary care providers. So, overall, when you take a look at patients being followed by subspecialists, we find approximately half to 60% of patients receive HCC surveillance, whereas those patients being followed by primary care providers—less than 1 in 10 receive HCC surveillance. And so this is a huge disparity in terms of the implementation of evidence-based screening in clinical practice.

Now, this is unfortunate because most patients with cirrhosis in the US are actually followed by primary care providers, really highlighting the importance of us to think through intervention strategies to improve the implementation of this in clinical practice.

As part of this systematic review, we also did highlight several intervention strategies such as provider reminder systems, recall systems, education strategies, outreach strategies that could be used to improve HCC screening in clinical practice, and we do hope that this will be facilitated and used in clinical practice in the future.

However, Screening Is Underused in Clinical Practice

- About three-quarters of patients with cirrhosis do not receive HCCscreening[a]
- The following factors have been shown to increase the likelihood of screening:
  - Management at subspecialty clinics
  - Patient, provider, and public health education initiatives
  - Reminder and recall systems
- The following factors have been shown to decrease the likelihood of screening:
  - Alcohol-associated cirrhosis
  - NASH-associated cirrhosis
  - Possible Black race
  - Presence of medical comorbidities
  - Ongoing alcohol use disorder



Proportion of patients undergoing screening

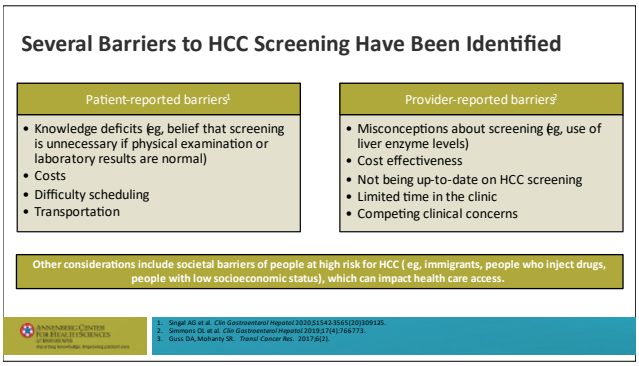
[a]In a systematic review of cohort studies, 118,799 patients with cirrhosis were evaluated for receipt of screening.

Wolf E et al. *Hepatology.* 2020;10.1002/hep.31309.

When we think of why HCC screening may not be used, we do know that there are many patient- and provider-reported barriers that have been identified in prior studies. So these barriers, both on the patient

and provider perspective, include some degree of knowledge deficits. We know that financial harms of HCC screening and cost can be important barriers from a patient perspective, difficulty scheduling, transportation, and all of these patient barriers can actually translate into lower screening rates in clinical practice.

Likewise, we find notable barriers on the provider perspective in terms of not being up to date in terms of the data for HCC screening, limited time in the clinic with competing clinical concerns. And as we think through how we can improve HCC screening in the future, I think we will need multilevel interventions that can act at each of these barriers to improve HCC screening.



Finally, we can see several examples of interventions that can improve screening rates. Once again, I mentioned some of these on that prior slide, but these interventions can range from something as simple as engagement and education strategies, electronic medical reminders, going all to more nuanced strategies such as mailed outreach strategies, doing population health programs in large health systems.

I think, overall, all of these interventions have been proven to be efficacious, and now I think the next step is to see how these actually work when we implement them in clinical practice.

ORANGE LINE: ASSESSMENT, DIAGNOSIS, & RISK STRATIFICATION

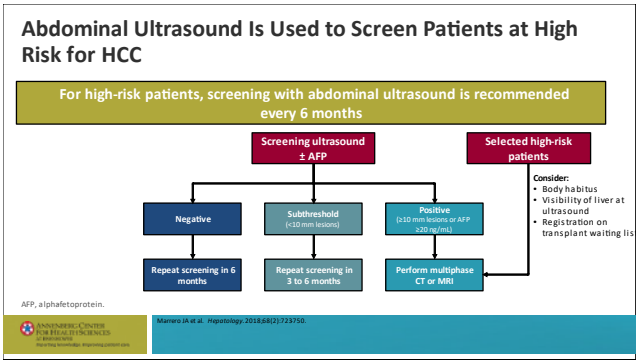
HCC Assessment & Diagnosis

Moving on to HCC diagnosis. As I referenced before, it's critical that we really implement HCC screening in clinical practice to identify patients with HCC at an early stage. When we think of our HCC screening strategy, HCC screening is typically done with an abdominal ultrasound with or without a serum blood test called alpha-fetoprotein, and this is done every 6 months. This strategy is really, once again, supported by high level of evidence, randomized control trial in patients with chronic hepatitis B, as well as several cohort studies in patients with cirrhosis.

When we think of the interpretation of patients who undergo screening, this can really be subdivided into 3 different interpretations: negative, subthreshold, or positive. When we think of patients who have negative screening results, for these patients, it's critical that we continue screening every 6 months, and this really highlights the continued high-risk state of patients with cirrhosis and the continued need for screening, even in the setting of negative testing upfront.

If patients have subthreshold results, ie, a lesion less than 1 cm on an ultrasound, or low-level elevations in terms of alpha-fetoprotein, they can continue being screened by ultrasound with or without alpha-fetoprotein, but we typically shorten the interval to approximately every 3 months to watch patients closer with this similar strategy.

If patients have a positive test, whether that's a lesion greater than a cm on the ultrasound, or an alpha-fetoprotein greater than 20 ng per mL, these patients do have a high risk of developing or having HCC, and it's typically at this point that we perform multiphase CT or a contrast-enhanced MRI as a diagnostic evaluation. Now we do know that there are some patients in whom ultrasound and AFP are at high risk for failure, whether that's patients with obesity, limited visualization on ultrasound, and those patients can be considered to bypass this screening strategy of ultrasound and AFP, and in selected patients, considered to go onto more of a screening strategy with contrast-enhanced MRI.



Now, in terms of our screening strategy, I talked about this ultrasound with or without alpha fetoprotein. It's my strong belief that the best test is to do the 2 tests in combination. We know that ultrasound is a good test, but unfortunately does miss many HCCs at an early stage if it's used alone. The sensitivity of ultrasound to find HCC at an early stage if it's used alone is actually less than 50%. When we take a look at all of the studies that have been done so far, the pooled sensitivity of ultrasound for early HCC detection, once again our goal of screening, is approximately 45%.

When you add alpha fetoprotein to the ultrasound, we see a notable and significant bump. And that sensitivity for early detection increases all the way to 63%. This is really, once again, highlighting the importance of using these 2 tests in combination. Of course we see a small drop off in terms of specificity, but that is actually not clinically notable. And so, once again, when you take a look at the diagnostic odds ratio, that diagnostic odds ratio is better using the 2 tests in combination, highlighting that this really is the best strategy moving forward at this time.

Now, one thing to note is that we see a sensitivity of 63% for early detection, clearly better than ultrasound alone, but far from optimal. And so there's been a lot of work that's really been looking at other biomarkers and other strategies to improve early detection in the future. And so it's my hope that we see notable advances over the next several years either in terms of novel biomarkers or novel imaging strategies.

There are several biomarkers that are currently being evaluated. One of these biomarkers is a panel called GALAD, which combines gender, age, and 3 biomarkers: AFP-L3, alpha-fetoprotein and then DCP. And using these 5 variables we're able to come up with a combined score called GALAD. And this score has actually been evaluated in terms of an early detection biomarker panel in a multicenter case control study with thousands of patients. And here you can see the data demonstrated in these different cohorts. And I think one of the things that's really exciting in these early data is that GALAD actually has a very high C-statistic for finding HCC at an early stage. And when we take a look at the sensitivity for early detection, the sensitivity of GALAD alone is often somewhere near this 70% mark. This panel still needs to be evaluated in future cohort studies, but these early phase 2 case control data are very promising.

Likewise, we've seen some data in terms of evaluating more nuanced imaging strategies. And so here you can see data from a cohort study that was done in South Korea evaluating contrast-enhanced MRI for early detection, compared to ultrasound for early detection. And I think, overall, this study followed several hundred people, 407 people over an 18-month period. And what we found, when you take a look at those patients who developed HCC over that 18-month period, is that sensitivity of MRI compared to ultrasound was significantly higher. So the sensitivity in terms of an early detection strategy was around 86% compared to a sensitivity of only 28% for ultrasound, with the vast majority of these patients not only being at an early stage, but in a very early stage. And so, once again, very exciting data for MRI. I do think that we need to have further data in terms of cost-effectiveness, but I think promising data in terms of this being a modality that we may evaluate for some selected subgroups in terms of a screening strategy in the future.

In Patients at High Risk for HCC, Liver-Specific Contrast MRI Improved HCC Detection Rates[1]

Surveillance method and category	Detection rate for any HCC (sensitivity)
Ultrasound	
4 (suspicious)	28%
3 (equivocal)	28%
2 (probably benign)	33%
1 (definitely benign/negative)	100%
MRI	
5 (highly suggestive)	61%
4 (suspicious)	86%
3 (equivocal)	88%
2 (probably benign)	88%
1 (definitely benign/negative)	100%

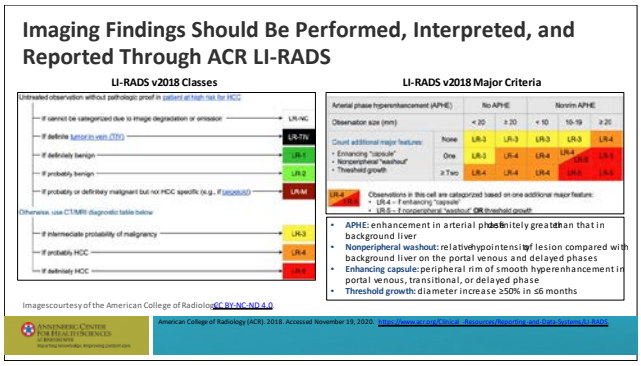
*In a trial of 407 patients with cirrhosis and annual risk of HCC >5% who underwent 1 to 3 biannual screening examinations with ultrasound and MRI with liver specific contrast

Kim SY et al. JAMA Oncol. 2017;3(4):456-463.

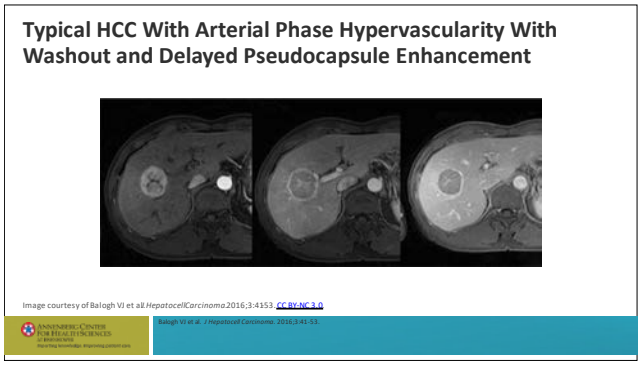
Now, moving on from this screening interpretation in terms of what we should do in terms of diagnostic evaluation. Once again, these patients who have a positive screening, whether that's ultrasound or alpha fetoprotein, do need evaluation with a multiphase CT or a contrast-enhanced MRI. And when we think of which test we should use, I think, overall, both 4-phase CT and contrast-enhanced MRI have similar performance, with a sensitivity or a diagnostic accuracy that really exceeds 80-90%. And so both are highly accurate tests that can be considered in these patient populations. And what I would say in terms of choosing between the 2, it really depends on local expertise. So, if your center is good at performing MRIs, I think MRI is a very good modality, but a good quality CT is better than a poor-quality MRI. And so, overall, I would say both can be considered in these patients with a positive screening test.

When we think of CT or MRI interpretation, one of the unique things about HCC is they can be diagnosed with high accuracy based on radiographic findings alone. Oftentimes we do not need to pursue a biopsy. There have recently been criteria that have been proposed called the LI-RADS criteria, which allows us to classify lesions into different categories ranging

from LR-1 or LI-RADS 1, definitely benign, all the way up to LI-RADS 5, which is definitely HCC. And you can see on the right-hand side of the slide the different criteria that go into classifying these lesions. And when we have patients who are having an LR-5 lesion, these patients have an accuracy of around 90% to 95% for being HCC and therefore often do not need a biopsy.

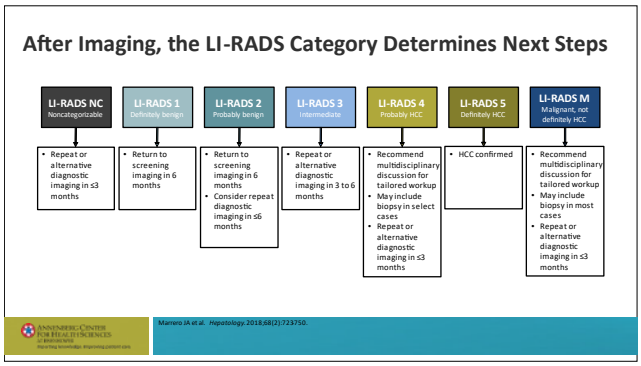


The central criteria that we use in terms of diagnostic features for HCC are arterial enhancement and delayed washout. And you can see these features very nicely on this image here where we see, on the left-hand side, arterial enhancement. And as we move to the venous phase and the delayed phase, you see not only washout where the HCC lesion becomes darker, but we also see a pseudocapsule enhancement, all classic features for HCC. And, once again, we would say that this patient has HCC with about a 95%-97% certainty, without doing a biopsy.



These accuracies were recently highlighted in this meta-analysis published in *Gastroenterology* in 2019, where looking at the literature, looking at the LI-RADS classifications, once again we can see LI-RADS 5 having a 94% accuracy for HCC, LI-RADS 4 being 74% for HCC, highly suspicious, but not quite at this level for LR-5, although the vast majority were HCC or malignant when actually worked up in terms of diagnosis. The other thing that you can see here is this category of LR-M, highly suspicious for malignancy, 93% of these are malignant with about one-third are HCC. Not having classic features for HCC but, once again, highly suspicious for malignancy, and these are lesions where we would classically biopsy them as you can see on this flow sheet in terms of a diagnostic workup. So, when we take a look at these LI-RADS lesions and you take a look at the recommended workup across the different spectrum, we can see that these lesions that are definitely or probably benign can continue to be followed in terms of ultrasound and AFP.

I think LI-RADS 3, this intermediate stage, is really one that we need better data on in terms of evaluation from a cost-effective standpoint. But really you can see that the guidelines recommend a pretty broad approach to this in terms of considering repeat or alternative diagnostic imaging anywhere from 3-6 months later, although we need further guidance in terms of when it's safe to go back to ultrasound and AFP on these patients. I think these patients with LR-4 to LR-M lesions, high risk of HCC, and really this is where multidisciplinary evaluation is needed in terms of thinking through the need or possible consideration of a biopsy or treatment just based on radiographic imaging alone.

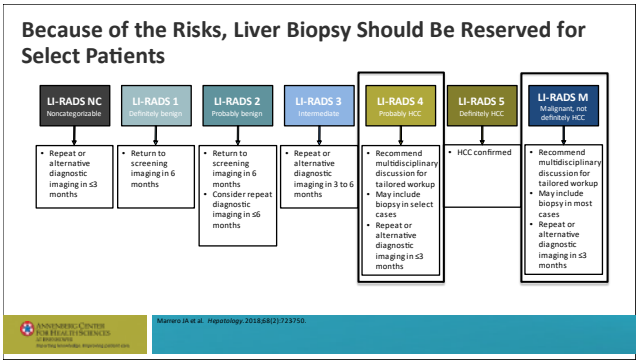


Role of Biopsy & Histopathology

Next, we'll talk about the role of biopsy in terms of HCC evaluation. As I mentioned, HCC is a unique cancer in that many of these lesions can be diagnosed radiographically. And this is actually done in the majority of HCC cases. Now, as I mentioned in the prior segment, if you have classic features of HCC on imaging, ie, a LI-RADS 5 lesion, this can be diagnosed radiographically with 95% to 97% certainty and you often don't need to go onto a biopsy. However, this doesn't mean that biopsy plays no role in HCC. And I think over this section we'll really talk about the considerations for biopsy and the potential role it may play in some patients.

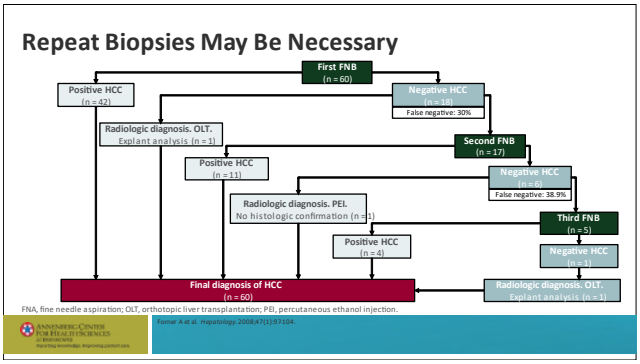
One may ask why not biopsy all patients even if you have classic features. And I think the reason this is the case is because we have to think of not only benefits of doing a procedure but also potential harms. And we know that liver biopsy is associated with several potential risks. And this can actually happen in up to 1%—if not slightly higher—of patients who undergo a liver biopsy. These risks can be relatively minor or they can be actually more significant. So some of the minor things that can happen is you can have some pain around that site. But you can actually have many serious complications that can happen, including hemorrhage, perforation of the gallbladder. You can have bile leak and bio peritonitis, you can have pneumothorax, hemothorax, and then you can have needle track seeding.

Although these complications are relatively rare, they can be clinically significant and devastating to that patient in which they occur. So, once again, when we think of the overall value of a liver biopsy, I think it's important for us to think about these risks whenever we think about pursuing this. Going back to the slide in terms of the LI-RADS classifications, I think liver biopsy really plays a major role for some patients with LI-RADS 4 lesions as well as LI-RADS M lesions. I can tell you our clinical practice in most patients with LI-RADS 4 lesions is to really opt for repeat or alternative diagnostic imaging in a short interval. There are some patients that we do consider for upfront biopsy where it will change immediate management. But most patients fall into this repeat diagnostic imaging section. In contrast, those patients with LI-RADS M lesions have a very high risk of having malignant lesions, 90% plus, and about one-third of those will be HCC. And differentiating what that malignant lesion is, is critical for us to have treatment decisions. And so those patients we are very aggressive in terms of obtaining pathology upfront and pursuing a biopsy in those patients.

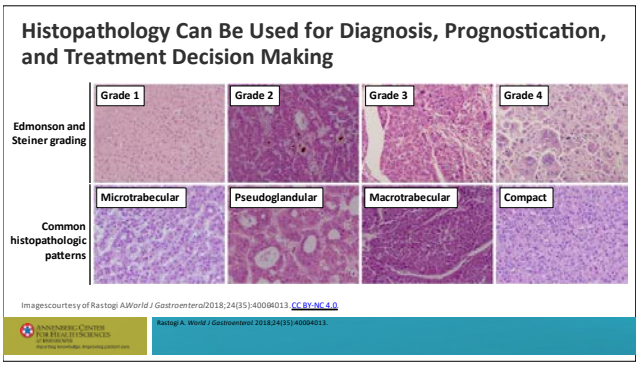


Now, one other thing that's worth noting here is that biopsies do not have a perfect negative predictive value. And what this means is that there will be patients in which you perform a biopsy, you get a negative result and it's a false negative. And so those patients in whom you have a suspicion of HCC or a malignant lesion, if you get a negative biopsy, it's important that you continue to follow them. And if you see changes that continue to make you suspicious

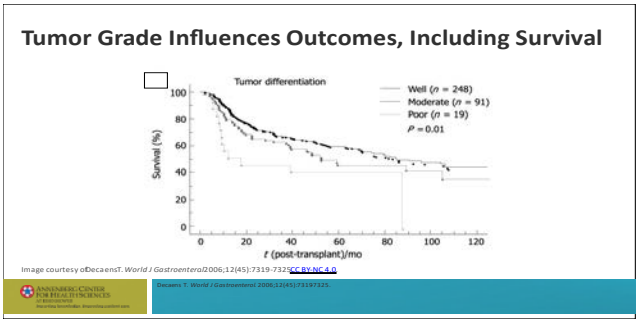
for HCC or malignant lesion, it's sometimes important to consider a second biopsy and may even be necessary to obtain a third biopsy. This was a nice study that came out of Europe several years ago that took a look at 60 patients who underwent biopsy for evaluation of HCC. And, once again, you can see that many of those patients—42 of the 60—were diagnosed on the first biopsy, but there was a subset that needed to have a second and third biopsy. So I think this is a very important point in those patients in whom you think biopsy is needed.



Now, histopathology in these patients once again can be important, not only in terms of diagnosis, but also obviously prognostication, treatment decision-making... The nice thing is that we now have very standard grading systems as well as subgroups of HCC that have been evaluated and identified. And there is now international standardization in terms of reading out HCC histopathology. The other thing that I would say is important here is that we've had increasing recognition that there are some patients who have mixed tumors, so mixed tumors for HCC and cholangiocarcinoma, or there are patients that you think have HCC but are actually found to have cholangiocarcinoma on biopsy. Once again, an important point as we think through the role of biopsy in terms of prognosis, as well as diagnosis and treatment decision-making.



Finally, in this section, one of the things that we are starting to increasingly recognize is the prognosis or the prognostication that can come from a biopsy. This was a nice study that actually took a look and showed the importance of tumor grade in terms of HCC-related outcomes, including survival. So you can simply divide HCC tumor grade into well, moderately, and poor differentiation, and not surprisingly those patients who have poor differentiation have significantly worse survival than those patients who have well-differentiated tumors. Now, how we implement this and use this for clinical decision-making and treatment decision-making I think is an evolving science. There have been risk scores that have used tumor differentiation for some treatment decisions in terms of like, for example, transplant eligibility, once again showing improved outcomes in those patients who have well-differentiated tumors compared to those patients who have poorly differentiated tumors. I think those things are all evolving, but I think will be important as we start to see biopsies being used in some patients, and starting to understand what role this may play in clinical practice.



BCLC Staging

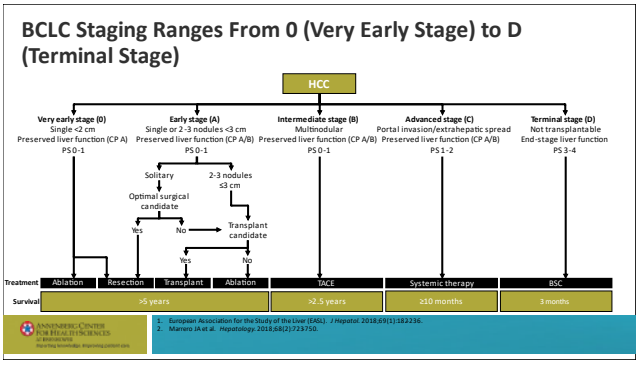
When we think of prognostication, one of the most important things that we do is to up front stage a patient who develops HCC. One of the important things to remember about HCC is that there is no universally accepted staging system. There's actually several staging systems that have been proposed, and different staging systems are used across the world.

Now, the most common—and probably the best accepted—staging system is the Barcelona-Clinic Liver Cancer (BCLC) staging system. The staging system, that clearly came out of Barcelona, has been evaluated and validated in multiple cohorts across the world, including cohorts not only from Europe but also from the United States. The nice thing about the BCLC is that this actually incorporates several key clinical criteria that had been shown to be important in terms of HCC prognostication. Not only tumor burden, like tumor size, tumor number, vascular invasion, distant metastasis, but also other factors such as the degree of liver dysfunction and ECOG performance status.

Now, this is important because we talked about the fact that the vast majority of patients who develop HCC do so in the setting of chronic liver disease, if not cirrhosis. And so these other factors are critical to consider when we think of prognostication for a patient with HCC. As you can see in this figure, the BCLC classifies people across different tumor stages ranging from BCLC stage zero or very early stage to BCLC stage A, BCLC-B, BCLC-C and then finally BCLC-D. I'm not going to go through each of these in detail here, but I think the thing that's worth pointing out is that you can see that these different stages are driven by differences in terms of tumor burden. You can see that on the top row for each of these different stages, as well as liver function going all the way from Child-Pugh A or Child-Pugh B and then end-stage liver function for those patients who are terminal stage, as well as ECOG performance status.

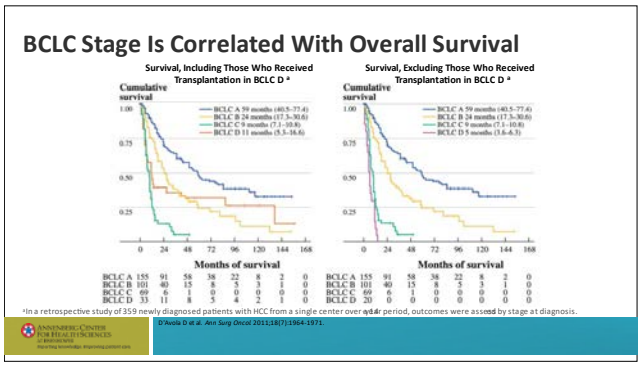
The lowest tumor burden, the best liver function, the best performance status on the left-hand side of the slide with these earlier stages of disease. And then those patients who have poor liver function, poor performance status, really fall into this terminal stage of HCC. You can see on the bottom row of the slide that this correlates not only with treatment eligibility, but also prognosis. So those patients who are found at an early stage have curative treatments available, including surgical resection, liver transplantation, local ablative therapies, and have a median survival well over 5 years.

Those patients with an intermediate stage can be treated with local regional therapies, whether that's chemoembolization, radioembolization … these liver-directed therapies that can give you good survival with a median survival above 2-3 years. Those patients with advanced stage disease: good liver function, moderate performance status but advanced tumor burden are typically treated with systemic therapy, whether that's targeted therapies or immunotherapy. And this is an area that we've seen tremendous advances in recently. And we used to have a median survival somewhere around the 1-year mark, but more recently we've seen median survival now extending all the way up to 18-24 months with systemic therapies in this space.

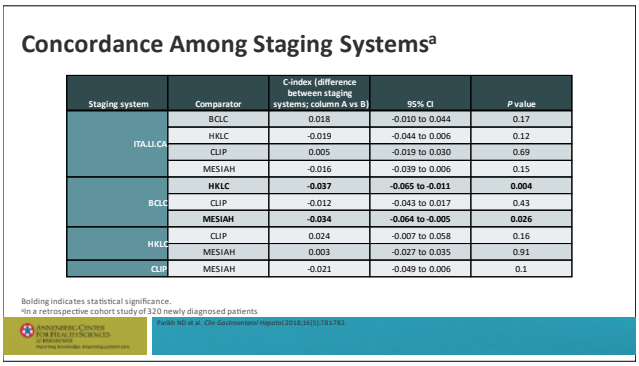


As I just reviewed, we can see that the BCLC is strongly correlated with survival. And here you can see data from several validation studies that continue to show the strong association between early-stage detection

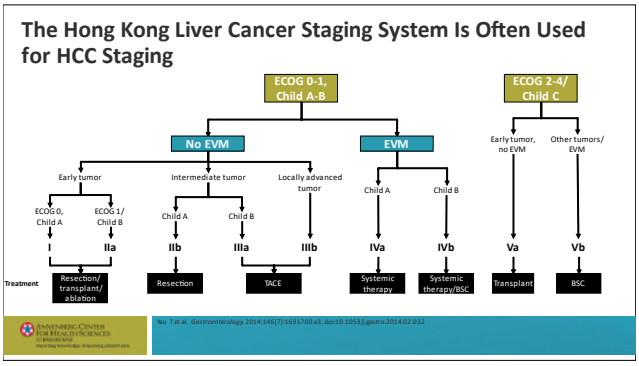
and long-term survival. Not only driven by lead time bias but really once again being driven by receipt of curative therapies that really nicely stratify prognosis for these patients.



Now, as I talked about, the BCLC is probably the best validated but there have been other staging systems that have been proposed. And here you can see some of those other staging systems listed in this table, whether it's the Italian staging system, the Hong Kong liver cancer staging system or the CLIP staging system. You can see here that these staging systems all have high C-statistics, so I think all of them are reasonable. In this validation study, you can see that there are some small differences in terms of C-statistics compared to some of these different staging systems, for example the Hong Kong liver cancer staging system having a higher C-statistic or accuracy than the BCLC in this validation study. However, I think that all of these have some degree of advantages and disadvantages, although the Hong Kong liver cancer staging system has slightly higher accuracy. As you can see here in this figure, it's much more complex than the BCLC. And really what it's doing is breaking down some of these stages into more granular subgroups.



And I think clearly this substratification of stages has some advantages in terms of accuracy, in terms of prognostication, but may have some difficulty in terms of complexity, and in terms of translation and implementation in clinical practice. I think, overall, when I take a look at these staging systems, I don't think that any one is right, I don't think that anyone is wrong. I think all have different advantages and disadvantages and can be complimentary as we think through what treatment can be considered for a patient in front of you.



I think, similarly, here you can see on the table the Italian staging system, relatively new, once again has more granular stages that can be offered and can be considered for your patient. And I think that this can be important in terms of giving perhaps more accurate prognostication and treatment decisions, but once again, potentially more complex in terms of implementation in clinical practice.

The ITA.LI.CA Tumor Staging System Is a Relatively New and More Granular Staging Option

Diameter of the Largest Nodule (cm)	Number of nodules	Vascular Invasion or metastases	Stage
≤2	1	No	0
≤3	2-3	No	A
2-5	1	No	A
3-5	2-3	No	B1
>5	1	No	B1
>5	2-3	No	B2
≤5	>3	No	B2
>5	>3	No	B3
Any	Any	Intrahepatic	B3
Any	Any	Extrahepatic	C

Farinati F et al. *PLoS Med*. 2016;13(4):e1002006.

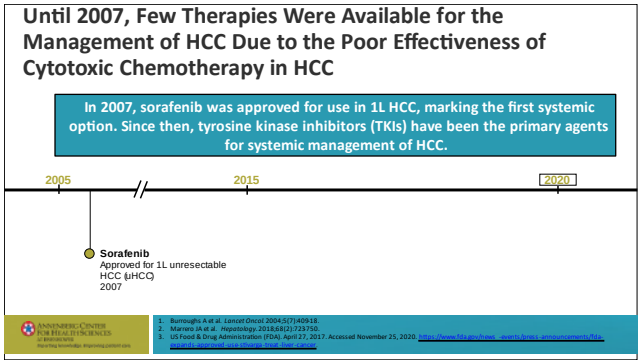
Stepping off this module I think that what I'd say, the most important thing it's important to mention, is to stage our patients. Actually, when we take a look at this and you take a look at charts, 50% of patients with HCC when seen in clinical practice fail to have any staging documented in clinical notes. So whether you use the BCLC, the Hong Kong or the Italian staging system or another staging system, I think the most important thing is to stage your patient so you can prognosticate and, importantly, determine treatment decisions. But the nice thing is that we have many of these offered, and I think we're going to see more staging systems come out in the future and cross comparisons between these as we move forward.

YELLOW LINE: SYSTEMIC THERAPIES

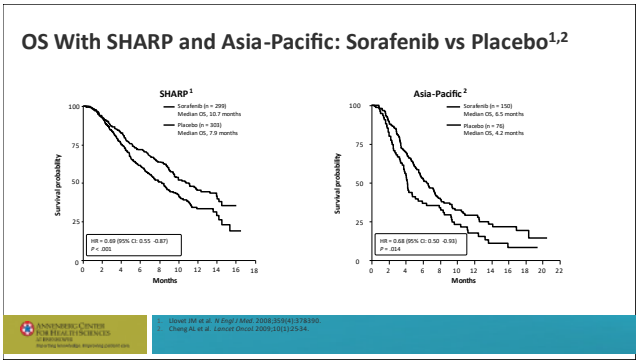
TKIs

We're next going to move into the current and emerging systemic therapies for unresectable HCC. Starting with the TKIs, the tyrosine kinase inhibitors. And this really is where systemic therapy in HCC started. So when we think from a historical perspective, I think it's important to remember that effective systemic therapy in HCC is relatively new. Until 2007, we actually had no therapies that were proven to be effective in advanced stage HCC. So you would see many providers try therapies simply because we had nothing else available.

In 2007, we had our first phase 3 trial that showed a benefit of systemic therapy in the advanced stage setting, and this was the SHARP and Asia-Pacific trial that led to the approval of sorafenib for first-line treatment of unresectable HCC.



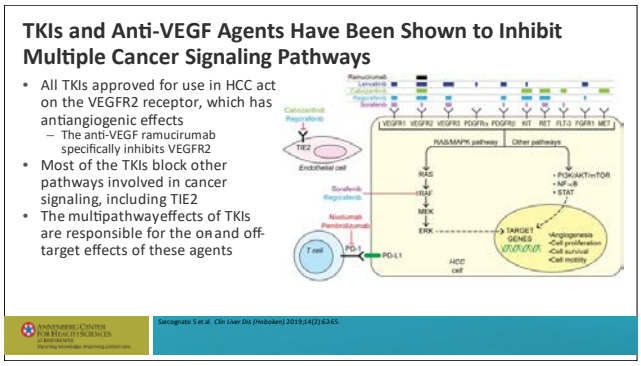
So here are our figures that I think many people have probably seen now over the last decade with the SHARP and Asia-Pacific trial, both demonstrating significant improvements in median overall survival, with the SHARP trial being the lead article in the *New England Journal* in 2008 for that issue, with an improvement in survival of 7.9 months for a placebo all the way up to 10.7 months for sorafenib.



When this trial came out, I think many of us expected that we would see a host of different therapies come out over the next several years. But actually the SHARP trial was followed by a drought of other therapies coming to market over the next decade. Negative trial over negative trial. But I think what really the SHARP trial and the tyrosine kinase inhibitors have importantly shown us is that we can have effective responses and improvement in survival by inhibiting multiple cancers signaling pathways.

Here on the schematic we can see several of those different pathways outlined, including different VEGF receptor pathways, RET pathways, FGFR pathways, MET pathways. All of these are important as we think through HCC pathogenesis, as we've discussed in our prior module. I think what you've seen is that these different therapies that have now been approved for first-line and second-line therapies all act on different pathways. So I think that all of these different agents that have been approved have found a way to be selective enough that they have limited their toxicity, but broad enough where they can have efficacy and inhibit enough pathways where we see improvements in overall survival. So I think that this figure really highlights some of the nice differences between some of these different agents, as we think through MOAs between the tyrosine kinase inhibitors. As we've started to see these tyrosine kinase inhibitors act upon these different pathways in a very safe and tolerable manner, the nice thing is

that we've seen, over the last 3-4 years, multiple agents come to market.



In 2017 we had the approval of our first second-line therapy, regorafenib. In 2018, we had approval of lenvatinib, which was noninferior to sorafenib in the frontline setting. And then more recently we had both cabozantinib and ramucirumab come out in the second-line setting. So we've seen multiple other tyrosine kinase inhibitors that have come to market.

Now, in this table we can see the results of the phase 3 studies that led to the approval of each of these agents. I briefly talked about the SHARP trial already. The REFLECT trial led to the approval of lenvatinib. This was a large noninferiority study with nearly 1000 patients that were randomized to sorafenib or lenvatinib in the frontline setting. What we saw was numerically higher survival with lenvatinib than sorafenib. Although this did not achieve statistical significance.

Given the large size of the REFLECT trial, the trial was able to prove noninferiority or a similar survival with lenvatinib, compared to sorafenib. This is what led to the approval of lenvatinib as an alternative frontline therapy for patients with advanced HCC. Now, one of the things that's noteworthy of the REFLECT trial—and I think one of the things that makes us interested in lenvatinib as an agent—is that we saw significant improvements in many of the secondary outcomes, including improvements in objective response rates, as well as progression free survival. So I think this is really exciting in terms of lenvatinib, and makes us excited as this gets evaluated in terms of combination therapies in the future.

Regorafenib was evaluated in the RESORCE trial, once again a second-line trial. Patients were required in this trial to tolerate sorafenib, given similar structures. So patients who were required to be on sorafenib for 20 or 28 days coming into the RESORCE trial at a dose of 400 mg a day but have disease progression. In these patients, regorafenib significantly improved survival, 10.6 months vs 7.8 months. 37% reduction in mortality in these patients.

The CELESTIAL trial led to the approval of cabozantinib. I think one of the important things about CELESTIAL is that this was a very broad patient selection, in terms of patients could have been sorafenib intolerant or disease progression on sorafenib. 27% of the patients actually had received 2 prior lines of therapy. So this actually not only gave data for cabozantinib in the second line, but also the third line. What we saw overall is significant improvement in survival, 24% reduction in mortality, 10.2 months with cabozantinib vs 8 months with placebo.

Finally, the REACH-2 trial evaluated ramucirumab. This was a trial that took a look at patients with elevated alpha-fetoprotein. So an AFP greater than 400. Ramucirumab was beneficial in these patients with an elevated AFP at time of treatment initiation, 8.5 months vs 7.3 months. I think this is important because this is the first biomarker selected trial, in terms of ramucirumab being helpful in these patients with an elevated AFP. I think noteworthy is ramucirumab was evaluated previously in the REACH trial in an all-comer patient population in the second-line setting and was not found to be helpful in those patients without an elevated alpha-fetoprotein. So once again, I think when we interpret where ramucirumab may fall it's really selectively in these patients with an elevated AFP, and it should not be used in patients with an AFP less than 400.

The other thing that's worth noting in terms of considerations in the second-line setting, there have now been subgroup analysis that have reported out of RESORCE as well as CELESTIAL, in terms of the benefit of regorafenib and cabozantinib in these patients with an elevated AFP. And these agents are also beneficial in those patients with an elevated AFP, ie, this more aggressive subtype. So really we have multiple therapies that are available and treatment options in this patient population with an elevated AFP.

TKIs and Anti-VEGF Agents Improve Outcomes for Patients With HCC

Drug (clinical trial)	Comparator	Target population	OS results
Sorafenib (SHARP)	Placebo	1L HCC, BCLC B or C, CP A or B	10.7 vs 7.9 months HR, 0.69 (95% CI, 0.55-0.87) P <.001
Lenvatinib (REFLECT)	Sorafenib	1L HCC, BCLC B or C, CP A or B	13.6 vs 12.3 months HR, 0.92 (95% CI, 0.79-1.06) Met criteria for noninferiority
Regorafenib (RESORCE)	Placebo	2L HCC, BCLC A -C, CP A	10.6 vs 7.8 months HR, 0.63 (95% CI, 0.50-0.79) P <.0001
Cabozantinib (CELESTIAL)	Placebo	2L HCC, CP A	10.2 vs 8.0 months HR, 0.76 (95% CI, 0.63-0.92) P = .005
Ramucirumab (REACH -2)	Placebo	2L HCC, BCLC B or C, CP A, ≥400 ng/mL AFP	8.5 vs 7.3 months HR, 0.710 (95% CI, 7.0-10.6) P = .0199

1. Llovet JM et al. *N Engl J Med.* 2008;359(4):378-90.
2. Bruix J et al. *Lancet.* 2017;389(10064):5666.
3. Kudo M et al. *Lancet.* 2018;391(10126):1163-1173.
4. Abou-Alfa GK et al. *N Engl J Med.* 2018;379(1):5463.
5. Zhu AX et al. *Lancet Oncol* 2019;20(2):282-296.

PD-1 Inhibitors

Tyrosine kinase inhibitors are really where systemic therapy in HCC started. Like many other cancer types, we've seen increased interest in terms of immune checkpoint inhibitors, and immunotherapy in terms of treatment options for HCC. We've seen a nice expansion of immune checkpoint inhibitors in this space. So when we think of single-agent immunotherapy, the single agent immunotherapy that's available for HCC includes nivolumab and pembrolizumab. These both received accelerated approval in 2017 and 2018 respectively, in the second-line setting based on promising phase 2 data.

When we think through immune checkpoint inhibitors, really I think of immune checkpoint inhibitors as taking our foot off the brake. We know that when HCC or any cancer presents, they actually have inhibitory signals that can decrease our immune response by binding several different receptors on T-cells, including the PD-1 PD-L1 access, as well as the CTLA-4 access. So what we find here is that these anti-PD-1 or anti-PD-L1 agents are able to block this inhibitory signal, thereby keeping our immune response active and able to therefore act against the tumor.

Immune Checkpoint Inhibitors Activate Immune Responses

- Inflammation and immune dysregulation are common in chronic liver disease and HCC
- Immune checkpoint inhibitors target PD-1 and CTLA-4, resulting in increased activated T cells and reduced levels of immunosuppressive cells

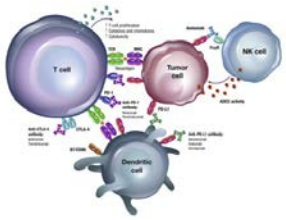


Image courtesy ofBaiebJ et al.*Cancer Treatment Rev.*2018;66:104113. CC BY-NC-ND 4.0

1. Kudo M. *Oncology.* 2017;92(Suppl 1):5062.
2. Taieb J et al. *Cancer Treatment Rev.* 2018;66:104113.
3. The Cancer Genome Atlas Research Network. *Cell.* 2017;169(7):1327-1341.e23.

When we think through the data that has been presented in terms of immunotherapy in HCC, this, once again, started in terms of phase 2 data. Here you can see data from the CheckMate 040 study in terms of phase 2 data with nivolumab. And I think the data that led to the accelerated approval of nivolumab in the second-line setting really was the high objective responses, and more notably the durability of those responses. For some of the TKI agents, particularly, for example, lenvatinib, we do see high proportions of responses, but those responses tend to be short-lived. And one of the exciting things with immunotherapy is we see durable responses that can last greater than 6 months, and in many patients even greater than 12 months. There was a lot of excitement as we went into the phase 3 trial, the CheckMate 459 study, that compared nivolumab vs sorafenib in the frontline setting. As you can see here in this table, nivolumab did result in longer survival, but unfortunately failed to reach statistical significance. Hazard ratio 0.85, *P*-value 0.0752.

Once again, there's limitations in terms of some of the transition into second-line therapies and other limitations in terms of the way the study was conducted. I think when we take a look at the strict

interpretation of this, this was unfortunately a negative phase 3 study. Although I think when we take a look at this, you can see that the study does highlight that single agent IO can have durable responses in about 15% to 20% of patients.

Although Single-Agent Immunotherapies Resulted in Response in a Phase 2 Trial, Primary End Points Were Not Reached in Phase 3

Nivolumab &CheckMateTrials

CheckMate 040 (Phase 2) [1]	
Patient population	1L or 2L HCC
N in dose-expansion phase	214
Objective response, n (%)	42 (20%)
Complete response, n	3
Partial response, n	39
Stable disease, n (%)	96 (45%)
Disease control rate, n (%)	138 (64%)
Median duration of response	9.9 months

CheckMate 459 (Phase 3) [2]	Nivolumab (n = 371)	Sorafenib (n = 372)
Median OS	16.4 months	14.7 months
	HR, 0.85 (95% CI, 0.72-1.02) *P* = .0752	
12-month OS rate	59.7%	55.1%
24-months OS rate	36.8%	33.1%
Objective response	15%	7%
Complete response	4%	1%
Partial response	12%	6%

1. El-Khoueiry AB et al. *Lancet*. 2017;389(10088):2492-2502.
2. Yau T et al. Presented at ESMO 2020. Accessed November 25, 2020. [Title illegible]

We see a similar story in terms of pembrolizumab in the second-line setting evaluated first in the phase 2 KEYNOTE-224 study. Once again, high objective responses in 18% of patients, durable responses and led to the accelerated approval of pembrolizumab in the second-line setting. Unfortunately, KEYNOTE-240, a phase 3 study, evaluating pembrolizumab vs placebo in the second-line setting, similar story to nivolumab in terms of improvements in overall survival numerically, 13.9 months vs 10.6 months. New data presented at GI ASCO in 2021 showed that these curves continued to be separated. However, given statistical considerations in terms of co-primary endpoints, as well as an early look at the data, unfortunately did not meet the prespecified alpha, so was regarded as a negative trial. However, when we look at this, I think once again, when you take a look at the responses, you do see once again, single-agent IO able to induce responses in 15% to 20% of patients and numerically better survival, just not statistically significant, all things being considered.

Although Single-Agent Immunotherapies Resulted in Response in a Phase 2 Trial, Primary End Points Were Not Reached in Phase 3

Pembrolizumab & KEYNOTE Trials

KEYNOTE-224 (Phase 2) [1]	
Patient population	104
Objective response, n (%)	19 (18.3%)
Complete response, n	4
Partial response, n	15
Stable disease, n (%)	45 (43.3%)
Disease control rate, n (%)	64 (61.5%)
Median duration of response	21.0 months

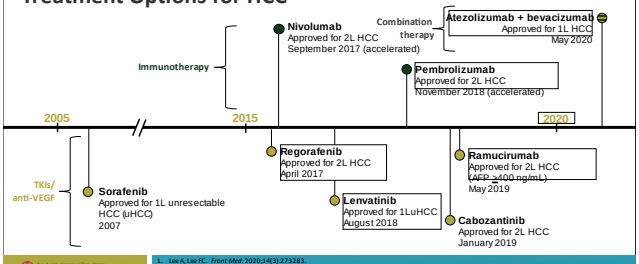
KEYNOTE-240 (Phase 3) [2]	Pembrolizumab (n = 371)	Placebo (n = 372)
Median OS	13.9 months	10.6 months
	HR, 0.781 (95% CI, 0.611-0.998) *P* = .0283 (not statistically significant by prespecified criteria)	
Objective response	18.3%	4.4%
Complete response	2.2%	0
Partial response	16.2%	4.4%

1. Kudo M et al. *J Clin Oncol*. 2020;38(4_suppl):518.
2. Finn RS et al. *J Clin Oncol*. 2020;38(3):193-202.

Combination Therapy

Overall, the field has moved on from single agent checkpoint inhibitor to combination therapy. And I think this is advantageous because although there was disappointment from the phase 3 studies, CheckMate 459, and KEYNOTE-240, that disappointed phase was relatively short. And this really was because the IMbrave150 study reported shortly thereafter. The IMbrave150 trial was the phase 3 study that led to the approval of atezolizumab and bevacizumab in the frontline setting. Now published in the *New England Journal* and officially approved by the FDA for first-line treatment of HCC.

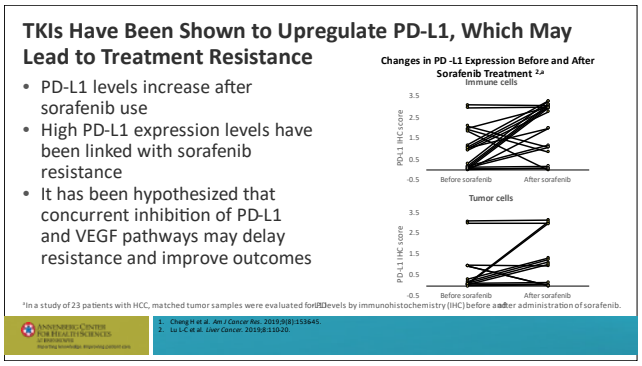
Combination TKI-Immunotherapy Regimens Are Emerging Treatment Options for HCC



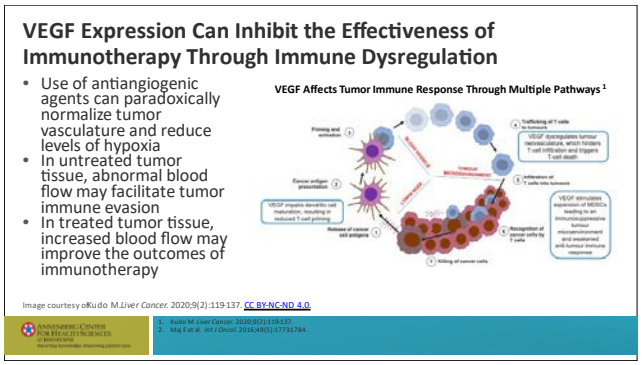
1. Lee A, Lee FC. *Front Med*. 2020;14(3):273283.
2. US FDA. June 1, 2020. Accessed November 27, 2020. [illegible]

Now, when we think of combination therapies, there's multiple reasons why this may actually be beneficial. I think when we thought of TKIs or tyrosine kinase inhibitors, initially, we thought really that their main action was acting upon those signaling pathways and inducing, for example, anti-angiogenic features. But I think there's been more understanding

that these tyrosine kinase inhibitors do have other activity, including upregulating PD-L1, which may actually augment immune checkpoint inhibitor activity. So the nice thing is that when we think of combination therapies, this really highlights preclinical rationale, why it may be helpful to use these combination therapies.

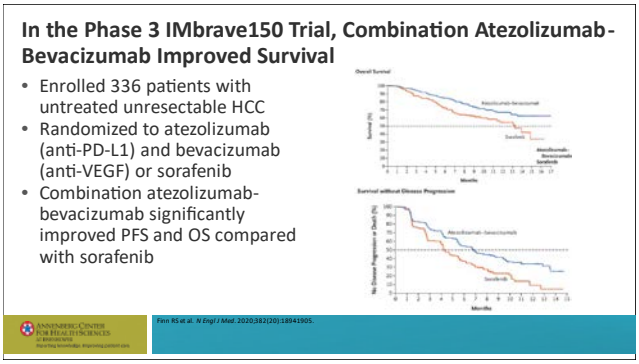


We see similar preclinical rationale while VEGF inhibition, through agents such as bevacizumab, may also be helpful in terms of combination therapies with checkpoint inhibition. We know that use of antiangiogenic agents can normalize tumor vasculature, reduce levels of hypoxia. We know that VEGF can actually lead to an immunosuppressive tumor microenvironment, and therefore suppressing this VEGF access can actually, once again, augment an immunomodulatory response and therefore augment checkpoint inhibitor therapy activity.



The nice thing is that this preclinical rationale actually translated into improved clinical outcomes in this phase 3 trial, the IMbrave150 trial, once again reported this past year—in 2020. Here we can see combination atezolizumab and bevacizumab being compared to sorafenib in this large, randomized control trial with just under 350 patients. The trial had co-primary endpoints of progression-free survival and overall survival. And at the first interim analysis, we see that the trial hit both co-primary endpoints. It had significant improvements in overall survival, as well as significant improvements in progression-free survival. When the trial first reported, median survival for the atezolizumab and bevacizumab arm had not been reached. We saw updated data being presented at GI ASCO in early 2021.

We see now we have a point estimate for the Atezo/Bev arm with a median survival of just around 19 months. So once again, compared to where we used to be with TKI therapy in the frontline setting, with median survival being somewhere around that 11-month mark, we now see significant improvements, now reaching median survival of 19 months with Atezo/Bev in the frontline setting. The other nice thing is that Atezo/Bev was very well tolerated. When you take a look at the AE profile, we see that the AEs were relatively rare and the Atezo/Bev was really well tolerated. When you take a look at the AEs that were reported, the most common grade 3-4 AE that was reported was really hypertension, which is relatively easy to treat and relatively unconcerning.



Well, one of the other endpoints of the trial was really quality of life and they took a look at the time to deterioration of quality of life. And quality of life was preserved significantly longer with Atezo/Bev than with sorafenib. So, another reason why this is really nice to consider in clinical practice for our patients. When we think of this, one of the most important things of the clinical trial in terms of patient selection was that this was used in patients with good liver function, Child-Pugh A disease. This was used in patients with minimal portal hypertension, and all patients were required to undergo an EGD within 6 months prior to going on Atezo/Bev. And when we think of the AEs and the tolerability, I think it's important for us to consider patient selection and not lose that when we apply this to clinical practice. So those patients with a high risk of bleeding, whether that's large viruses, untreated viruses, significant portal hypertensive gastropathy, were not included in the IMbrave150 trial. So once again, for us to have that good quality of life and low AE and tolerable AE profile, very important for us to consider as we apply this to clinical practice.

I think the IMbrave150 trial was really the first trial that showed the benefit of combination therapy. There are several other trials that are in the pipeline here in this table. You can see some of these being delineated. The HIMALAYA trial, evaluating durvalumab and tremelimumab in the frontline setting. You see COSMIC-312 evaluating atezolizmuab and cabozantinib in the frontline setting. You see LEAP-002 evaluating lenvatinib and pembrolizumab in the frontline setting. All of these are really supported by early promising phase 1 and phase 2 data. I think all of us are really excited about what these trials will show. And I think that we will probably see these being presented over the next 1-2 years, and I think we're going to see really an explosion of combination therapies coming onto the market.

Unresectable HCC Treatment algorithms

When we think of treatment algorithms, I think we're a little bit in the calm before the storm when we think about how we can apply this to clinical practice. So when we think of this in terms of an overall treatment algorithm, I think it's really important to remember that in systemic therapies we've seen notable advances, but this really falls into a larger spectrum of potential treatment options.

So I can't emphasize enough that if patients are found at a very early stage or an early stage, we have curative therapies available, whether that's liver transplantation, surgical resection in some patients, local ablative therapies. And these curative therapies are associated with 5-year survival, well over 60%. Likewise, if you're found to have liver-localized disease, many of these patients can be treated with liver-directed therapies—chemoembolization, radioembolization, once again associated with median survival approaching 3 years. So I think these therapies should continue to be used and considered in these patients with liver localized disease. Once again, we've reviewed all of the exciting advances that we've seen in patients with advanced AJCC vascular invasion or distant metastatic spread. So I think that when we think of surgical resection, once again, curative therapy, you get rid of the tumor.

Treatment With Curative Intent Is the Preferred Option for Candidate Patients

Potentially curative			Extends survival
Surgical interventions	**Percutaneous ablation**	**Transarterial therapies**	**Systemic therapies**

• **Resection:** surgical removal of the tumor along with surrounding liver tissue
• **Liver transplantation:** replacement of the liver with a healthy donor liver
	• **Ablation:** destruction of liver tumors using extreme temperatures or chemicals:
	  • Percutaneous ethanol injection (**PEI**)
	  • Radiofrequency ablation (**RFA**)
	  • Microwave ablation (**MWA**)
	  • **Cryoablation**
		• **Transarterial chemoembolization (TACE):** blockade of blood flow to the liver with concurrent delivery of chemotherapy
		• **Radioembolization (yttrium-90 [Y90]):** delivery of high-dose radiation to the liver
			• **TKIs and anti -VEGFs:** targeted therapies that inhibit angiogenic pathways
			• **Immunotherapy:** checkpoint inhibitors
			• **Combination therapy:** combination of targeted and immunotherapy

1. Marrero JA et al. *Hepatology*. 2018;68(2):723-750.
2. EASL. *J Hepatol*. 2018;69:182-236.
3. National Comprehensive Cancer Network (NCCN). Hepatobiliary cancer version 5.2020. August 4, 2020. Accessed November 27, 2020.

This can be considered in patients typically with unifocal disease that's limited to the liver. I think, most notably, these patients have to have good liver function without significant portal hypertension. These patients can be treated with a median survival well over 5 years. The one thing to note is that you do leave behind the cirrhotic liver. So these patients are at high risk of recurrence. So it is something that we need to continue posttreatment surveillance in these patients. As we'll talk about, I think this is why we're really seeing the push towards considering adjuvant and neoadjuvant therapies in this patient population.

The other curative therapy that we have in terms of surgical therapies is liver transplantation. The historic criteria that we used in terms of liver transplantation in the US was the Milan criteria, determined to have the best outcomes in terms of liver transplantation, and you can see those delineated on this slide. I think as we've had more experiences with liver transplantation, we see experiences in patients with larger tumor burden that can be effectively treated, can be downstaged into Milan criteria, ie, tumor responses where we see shrinkages in the cancer, and these patients actually have very good survival after liver transplantation, and I think once again, should be considered the standard of care if and when possible. Liver transplantation not only as a cure for the cancer, but as a cure for the underlying cirrhosis, has the best long-term survival, lowest risk of HCC recurrence. So once again, I would strongly encourage us to remember that any patient who can be treated with liver transplantation likely should be treated with liver transplantation.

Milan Criteria Can Be Used to Determine Transplantation Eligibility

Milan criteria[1]:

1. Single lesion ≤5 cm or ≤3 separate lesions, none larger than 3 cm
2. No evidence of vascular invasion
3. No regional nodal or distant metastases

Downstaging involves locoregional therapy to attempt to reduce tumor burden to within the Milan criteria. The following downstaging cases can result in priority listing[2]:

- Single lesion, <8 cm in size
- 2-3 lesions, <5 cm
- 4-5 lesions, <3 cm

1. Mazzaferro V, et al. *N Engl J Med*. 1996;334(11):693.
2. Yao FY, et al. *Hepatology*. 2015;61(6):1968-1977.

When we think of local regional therapy, this was a nice systematic review that was published recently that looked at the outcomes of patients undergoing local regional therapy. This was specific to chemoembolization, but I think we see similar results in terms of radioembolization in terms of survival. I think, overall, we know that the median survival for chemoembolization and radioembolization is right around this 3-year mark, and this continues to play an important role for patients with liver localized disease where we see notable responses and good survival.

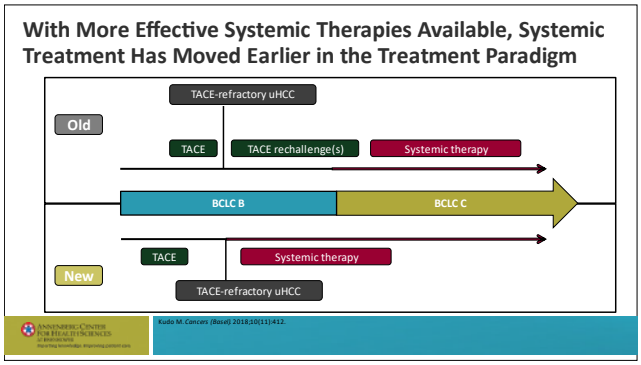
Outcomes With Locoregional Therapy

Author and year	Patients (n)	OS (%)		
		1-year	3-year	5-year
Lencioni et al, 2005				
Child-Pugh A	144	100	76	51
Child-Pugh B	43	89	46	31
Tateishi et al, 2005				
Child-Pugh A	221	96	83	63
Child-Pugh BC	98	90	65	31
Choi et al., 2007				
Child-Pugh A	359	NA	78	64
Child-Pugh B	160	NA	49	38
N'Kontchou et al, 2009				
BCLC resectable	67	NA	82	76
BCLC unresectable	168	NA	49	27

Lencioni R. *Hepatology*. 2010;52(2):762-773.

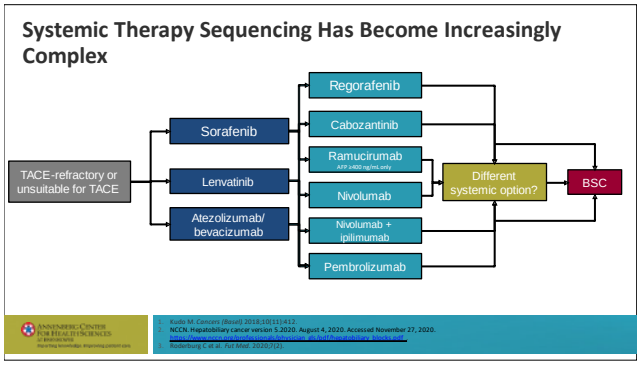
Now, as we've seen advances in the systemic therapy space, I think that there have been considerations in terms of when should systemic therapy be started. I think all of us have had increased recognition that there are patients who are TACE refractory or TACE intolerant, and those patients should move on to systemic therapy earlier, even if they continue to have liver-localized disease. I think what this means is that those patients who either have liver dysfunction related to chemoembolization, or have a tumor progression related to chemoembolization, we are starting to see earlier implementation of systemic therapy so we can take advantage of all of these exciting advances that we've seen in the advanced stage setting. So I think many of our multidisciplinary settings have become more cognizant of this. I think we're going to see more and more data come out in terms of when is the appropriate time to transition from local regional to systemic therapy.

The other thing that I think is not delineated on this slide, but is of increasing interest, is that there are trials that are looking at combination therapies, combination therapies in terms of combining systemic therapy with chemoembolization, as well as looking at systemic therapy in the adjuvant and neoadjuvant setting. I think those trials are relatively early. We're starting to see more phase 2 studies, but we are starting to see phase 3 studies being launched and I think those data will also become available over the next couple of years, and I think would also be an area of immense need and would really help us in terms of improving the overall prognosis for these patients.



Now, when we think of this, I mentioned we're in the calm before the storm earlier in this module. I think it's because we currently have some degree of semblance of sanity in terms of a number of limited options. Once again, atezolizumab and bevacizumab really being the standard first-line therapy in all patients who can be considered. Sorafenib and lenvatinib being considered alternative agents if you're not eligible for atezo/bev, and then other agents available in the second- and third-line setting.

I think in terms of optimal sequencing, of course, we do need better data and it'd be nice if we had biomarkers to be "smarter" about our treatment choices. But I think we're going to see more and more agents come to market, including other doublets that I've already referenced. I think then it's going to be increasingly difficult, increasingly complex in terms of choosing between these different agents in terms of what is the best agent for your individual patient in front of you.

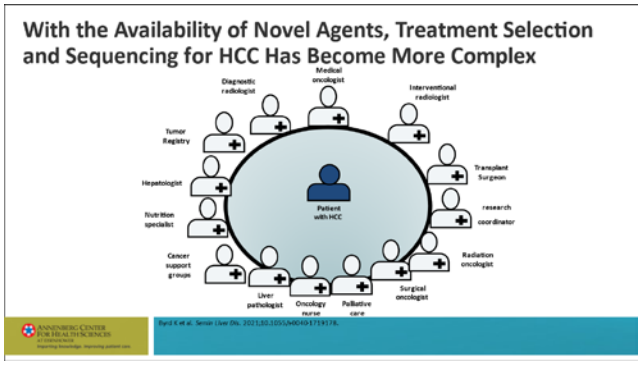


This is obviously a good problem to have. Even though life has become potentially more difficult in terms of treatment options, clearly, this is a huge advance for providers and patients in this space. We made tremendous advances over the last 12 years, moving from single agent sorafenib as the only agent available, to now having several therapies in front of us. Once again, in parallel, seeing tremendous advances in terms of our prognosis for HCC patients going all the way from a median survival of around 11 months now starting to approach closer to that 1.5-2-year period, even for patients found at an advanced stage setting.

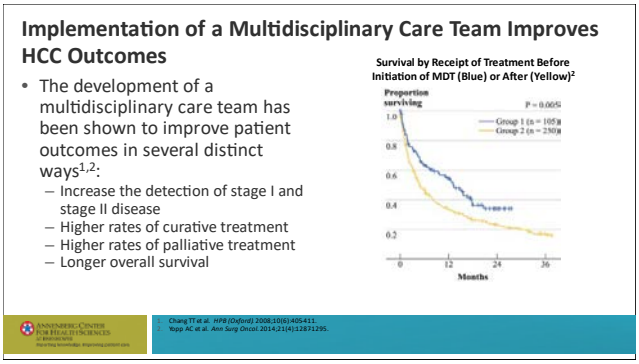
BLUE LINE: MULTIDISCIPLINARY CARE

Multidisciplinary care team

So, as you've seen from the discussion of the different treatment options, we have multiple options available for our patients with HCC ranging from surgical therapies, to local regional therapies, to systemic therapies. All of these happen in the setting of chronic liver disease. When we think of making treatment decisions for HCC, there's been increasing recognition that it is critical for us to have a multidisciplinary format. These multidisciplinary formats can either be a multidisciplinary clinic or a multidisciplinary tumor board, but I really think that we need to have formats where you can have all of these different providers sitting around talking about your patient with HCC, and really you need to have multiple different folks from different specialties that are engaged to make the best treatment decisions.



Now, the important thing when we think of multidisciplinary care is this isn't just a nice concept in terms of HCC. This is actually something that's evidence based. There have now been several studies that have shown improved outcomes with the implementation of multidisciplinary care with now over 5 studies that have shown several important improved outcomes, including higher rates of curative treatment, higher rates of any treatment, improved time-to-treatment, and, most notably, longer overall survival. This has really taken in multiple different ways, whether propensity-matched analysis, adjusted analyses. The data really do suggest that multidisciplinary care is beneficial and should be considered standard of care for our patients with HCC. As we talked about, we're really going to a world where these therapies are not discreet steps, but really we continue to think through transitions in therapy, as well as combination therapies. As we go to this whole new world of HCC therapy, multidisciplinary care is only going to become more and more important as we move forward.



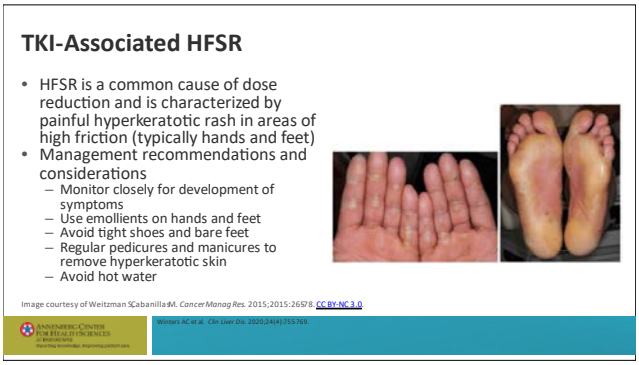
MKI AEs

Now, the other thing in terms of the benefits of multidisciplinary care is not only treatment decisions, but also adverse event management. So each of these therapies that we consider have potential AEs, although, once again, generally manageable and generally relatively rare. When we think of the tyrosine kinase inhibitors, the tyrosine kinase inhibitors, I think of there being common, but manageable, adverse events. Although, it's important for us to watch these and it's important that these can be dose limiting, ie, it's important that we may have to reduce the dose or sometimes discontinue tyrosine kinase inhibitors temporarily to keep our patients on therapy. Now, the most common related AEs that we see include diarrhea, fatigue, hand-foot reaction and hypertension. Now, once again, all of these can be managed. All of these can be prevented, but it is something that we continue to monitor for.

As we think through all these AEs, the first that we want to talk about is diarrhea. Diarrhea is reported in more than one-third of patients who receive tyrosine kinase inhibitors, and there are some simple things that we can do. The first, obviously, is to talk about this with our patients so they let us know if this occurs. Now, in those patients who otherwise have some degree of hepatic encephalopathy, if they're on lactulose, it's always important for us to adjust that lactulose dosing. If that patient's not on rifaximin, you can consider adding rifaximin so you can further reduce that dose of lactulose, thereby minimizing any lactulose-induced diarrhea.

You can limit other things that can exacerbate the diarrhea—caffeine, dairy products. Then you can use other agents like loperamide for those patients with diarrhea. I think one of the important things is to make sure that our patients don't just stop drinking and eating because, obviously, this won't stop the diarrhea given the fact that it's medication-induced, and this can obviously quickly result in dehydration and volume depletion if they just simply stop eating and drinking. We want to use other management styles to really treat the diarrhea.

Now, hand-foot skin reaction is a common cause of dose reduction and can actually be quite debilitating if we miss this at an early stage. So this really highlights the importance of seeing our patients and it's almost like doing those diabetic foot exams and where you have to take a look at your patient, look at their hands, feet, and the patients actually have to do this on a regular basis. So they tell you about this if and when it occurs. Now, there are some things that we can do upfront. Obviously, as I talked about, it's important for us to monitor. Patients can use urea-based creams and emollients to basically help prevent this from happening. They can avoid tight shoes and bare feet once again, to prevent this from happening, avoiding hot water. Here in Texas, I make sure that our patients avoid tight-fitting boots that can also exacerbate this. So there's some small things that you can do with your patients. But I think the key thing is if it happens, it's important that we find this at an early stage, be aggressive in terms of our urea-based creams, potential dose reductions to really prevent this from getting quite bad, because if it gets bad, you could actually see people who can't walk, who can't hold things in their hands. So this can be quite debilitating if it gets quite severe. The key thing is to prevent it and to find this at an early stage so you can be quite aggressive in terms of management.



TKI-associated hypertension is reported about one quarter of patients. I think this is something that we're used to seeing just in general and in other patients. Of course, not necessarily in our cirrhotic patient population because these patients tend to, if anything, have lower blood pressures at baseline, but otherwise relatively simple to manage. It's really just highlighting the importance that this can happen. We do need to monitor their blood pressure, obviously take a look at those readings, and then initiate antihypertensives if and when needed.

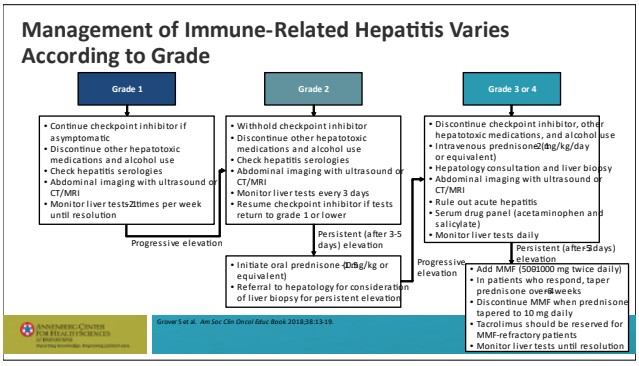
TKI-associated high hepatic dysfunction. There are some patients that can be seen with elevated levels of bilirubin, maybe some low-level transaminases. I think that the key thing, if you see this of course, is to really determine if this is related to the TKI or if that patient has liver dysfunction and you're really seeing, unfortunately, that patient progress in terms of their liver dysfunction, and if this is a patient that you need to start having prognostic discussions in terms of their overall survival. But I think from an HCC patient population, of course, this is something that will be

monitored regularly, and I think it was just basically trying to determine why this is happening and to have that discussion with your patient.

irAEs

Now, when we think of adverse events related to the immune checkpoint inhibitors, I think these AEs tend to be rare, but I think in contrast to TKIs where they're common and they're mild and generally manageable, I think the AEs that you see with immune checkpoint inhibitors are rare, but they can be quite significant and they can be quite severe. So different boxes to consider. Now, when we find this, I think that it's important for us to have, even though they're rare, for us to have a high level of suspicion when we have people on immune checkpoint inhibitors and to find these at an early stage and to be aggressive in terms of our management, withholding the agents, plus/minus steroids, if and when needed. I think once again, in terms of this severity comment, these things can be manageable, but if missed at an early stage, can be quite significant and even induce mortality in some patients.

So when we think about this from an HPC perspective, I think one of the things that was really a worry was immune mediated hepatitis. I think the nice thing that we saw come out of the CheckMate 459, the KEYNOTE-240, as well as now, the IMbrave150 trials, is in these 3 studies, the incidence of immune-mediated hepatitis was relatively similar to those seen in other tumor types. So we don't see notably higher incidence of immune-mediated hepatitis. So once again, relatively uncommon, and most of those cases being relatively mild in nature. If you see this, it's important for us to grade the severity and that's done so comparing to baseline liver enzyme elevations. As you can see here on this diagram, in terms of management, once you grade the degree of immune-mediated hepatitis, this allows you to see if you need to basically just hold the checkpoint inhibitor and/or if you should consider starting steroids. Those steroids are typically not your pred pack dose of 40 mg. Oftentimes, we have to use higher doses of steroids. So I think that's just one thing to consider in terms of management. For those patients who have more severe immune-mediated hepatitis or refractory immune-mediated hepatitis, you may consider adding other agents, including MMF at a dose of 500 to 1000 twice daily. So once again, just worthwhile thinking of this algorithm and keeping it in your back pocket if you see people with immune-mediated hepatitis.



It's important for us to consider other causes of elevated LFTs, whether that's liver dysfunction, which typical looks different than immune-mediated hepatitis, but also other causes like drug-related liver injury, including herbals, other infections that can occur, including a flare of an underlying hepatitis B if a patient isn't on antiviral therapy, which should be considered before starting any kind of systemic therapy. But I think, of course, these things should be considered and this treatment algorithm for steroids, etc, should only be done if we really feel confident in our diagnosis for immune-mediated hepatitis.

Now, I don't have slides in terms of going over the rest of the immune-mediated events that can occur, but I do think that it's important for us to keep in mind that many other immune-mediated events can occur, including endocrinopathies, pneumonitis, colitis. These things are all possible, even whether that's in the setting of another cancer type being treated with checkpoint inhibitors or a patient with HCC. So if you see any symptoms that can be nonspecific—

shortness of breath, cough, increase in fatigue, some mild diarrhea or blood in the stool—in addition to the other things that can happen, I think it is important to think about these other immune-mediated events, evaluate as needed, and then start treatment if and when indicated.

So overall, for this section, I'd say that it's important, as we start these patients on therapy, whether that's tyrosine kinase inhibitors or checkpoint inhibitors, obviously it's important that we continue to monitor these patients, identify AEs early, be aggressive with our management strategies so we can keep these patients on therapies that can improve survival. As we started this section, I think that not only initial treatment decisions, but even monitoring and continued treatment decisions on therapy should always be done in a multidisciplinary format, not only in terms of AE management, but also stage migration and reconsiderations of different therapies. As you have people that progress, so move to the right side and need to use more, for example, local regional and systemic therapy, or to the left, ie, you have people who have responses, so you have people who start on systemic therapy and then have progressive responsive disease where you may consider local regional or surgical therapies. These kinds of decisions are all made best in a multidisciplinary format as you continue to follow the patients on therapy.