Surveillance for Hepatocellular Carcinoma: How Can We Do Better?

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This is to acknowledge that Amit Singal MD has disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Singal will not be discussing off-label uses in his presentation.

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Purpose/Overview: The purpose of this talk is to provide an overview of hepatocellular carcinoma (HCC) care that are important from a primary care physician perspective, with a focus on epidemiology and the importance of HCC surveillance in at-risk patients.

HCC is the third most common cause of cancer related death worldwide and one of the most common causes of death in patients with cirrhosis. Although it has a lower incidence in the United States, its incidence is dramatically on the rise. Patients with cirrhosis, from any etiology, are the primary at-risk population, with an incidence of 2-5% per year. Although HCC can present symptomatically, including hepatic decompensation, it typically is asymptomatic at time of diagnosis. This highlights the importance of routine surveillance in at-risk patients.

Accordingly, the American Association for the Study of Liver Diseases (AASLD) has recommended ultrasound every 6 months in patients with cirrhosis. Although alpha-fetoprotein (AFP) is no longer included in the AASLD, guidelines, this is based on poor evidence. Most notably, there is increasing evidence supporting a gap between ultrasound's efficacy and effectiveness so AFP significantly improves the sensitivity of surveillance in clinical practice. As demonstrated in a RCT among patients with HBV and several cohort studies among patients with cirrhosis, HCC surveillance is effective at detecting tumors at an early stage, when curative therapies are available, and leads to significantly improved survival. Multiple analyses have also shown that surveillance using ultrasound, with or without AFP, is cost-effective. Unfortunately, HCC surveillance continues to be underutilized in clinical practice, with less than 20% of at-risk patients undergoing surveillance. This is related to multiple causes, including under-recognition of liver disease and cirrhosis in nearly 40% of patients; however the most common reason is a failure to order surveillance in those with known cirrhosis.

The diagnosis of HCC is typically made by radiographic means and biopsy is only necessary in a minority of patients. Furthermore, patients with lesions < 1 cm have a very low risk of HCC and can be initially followed by short interval ultrasonography. Patients with Child Pugh C cirrhosis and/or poor performance status are not eligible for any therapies and therefore do not benefit from surveillance.

Educational Objectives:

1) To understand the epidemiology of HCC worldwide and in the United States
2) To know the optimal tools and surveillance interval for HCC surveillance
3) To gain an understanding of the underutilization of HCC surveillance in the United States

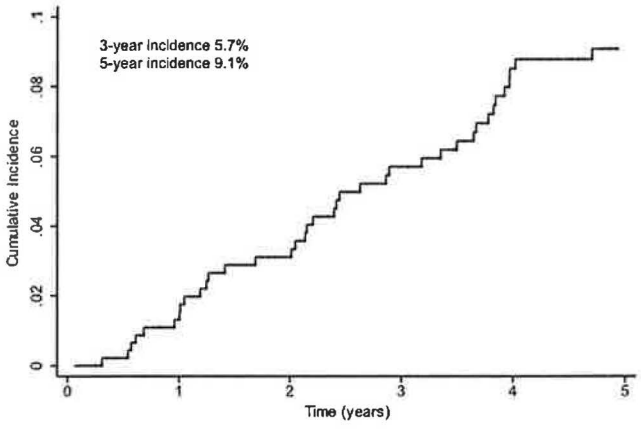
Disease Burden

Hepatocellular carcinoma is currently the third most common cause of cancer related death worldwide, resulting in over 500,000 deaths per year [1]. Furthermore, it is one of the leading causes of death among patients with cirrhosis. There is substantial geographic variation, with the highest incidences in East Asia and Africa, largely driven by the high rates of hepatitis B in those areas. It has an intermediate incidence rate throughout Europe and in the United States, with the thirteenth highest incidence rate among solid tumors in the United States. Within the United States, there is marked geographic variation in HCC incidence, with a North-South gradient and one of highest rates in the state of Texas.

The incidence of HCC has been on the decline in some areas such as China due to a reduction in HBV rates with more widespread vaccination programs. On the other hand, the incidence of HCC has been on the rise in both Europe and the United States. Over the ten-year span of 1995 to 2004, HCC actually had the largest increase in incidence among solid tumors in the United States [2]. Similarly, it had the largest increase in mortality of all solid tumors over the same ten-year period. The incidence of HCC has been rising in both Europe and the United States, largely due to the growing prevalence of hepatitis C cirrhosis. A molecular clock study indicated that the epidemic of hepatitis C virus (HCV) in the United States started in the 1960s and peaked in the late 1980s[3]. Due to the lag time between the onset of infection and the development of cirrhosis, the authors postulate that the incidence of HCV-related HCC will continue to increase over the next 20 years.

At-Risk Population

One of the necessary criteria for an effective surveillance program is identification of an appropriate target population who is at high-risk for the disease [4]. Based on cost-effectiveness data, surveillance should likely be offered to patients who have greater than a 1.5% risk per year of developing HCC. Cirrhosis is the most important risk factor for the development of HCC, with an annual risk of 2-7%[5] (Figure[6]). HCV and hepatitis B virus (HBV) are the major agents of etiology that lead to the development of HCC. HCV-associated cirrhosis is the causative agent largely responsible for the increase in incidence of HCC in the United States and Europe. However, HBV is the leading cause of HCC worldwide, particularly in Asia and Africa. Alcoholic cirrhosis is



another well-established major etiologic risk factor for the development of HCC. An association between nonalcoholic liver disease and HCC has also been established more recently, although the annual incidence rate has not been well established given a paucity of prolonged natural history studies. Given the growing problem of obesity and diabetes, the incidence of NASH-related HCC will likely continue to increase over the next several years. Other etiologies of chronic liver disease, such as hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, and alpha-1 antitrypsin deficiency, are less common causes of chronic liver disease, with prevalence rates of 1–8% in patients with HCC (Table[7]). Furthermore, improvements in the survival of patients with cirrhosis due to better specialty care may further increase the number of individuals at risk for developing HCC.

Surveillance recommended		
Population group	**Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)**	**Incidence of HCC**
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

Among patients with cirrhosis, male gender, older age, alcohol and tobacco consumption, obesity, and diabetes are factors associated with an increased risk of HCC[8, 9]. In patients with chronic HBV infection, a baseline HBV DNA level of greater than 100,000 copies/mL increases the risk of HCC ten-fold[10]. This biologic gradient of HCC risk in relation to HBV DNA level suggests that persistent viral replication increases the risk of HCC. A prospective cohort study of patients with cirrhosis found that prothrombin activity less than 75% of baseline, age of more than 55 years, platelet count less than 75 mm3, and presence of HCV were independent risk factors for developing HCC[11]. When the researchers stratified patients into a high-risk group (presence of these factors) and a low-risk group (absence of risk factors), the 5-year cumulative incidence of HCC was 30% for the high-risk group and 4% for the low-risk group (P<.0001). Further studies should be performed to determine whether stratification according to risk factors is beneficial for delineating a subgroup of high-risk patients at whom surveillance can be targeted.

Clinical Presentation

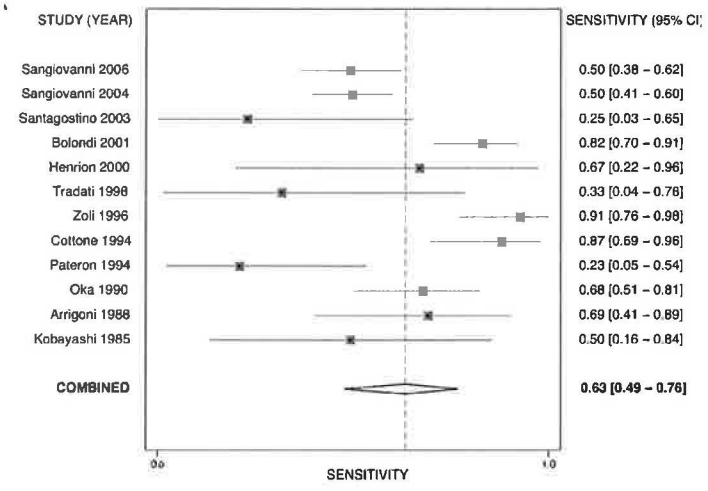
The clinical presentation of HCC varies considerably and is often dependent on the degree of hepatic reserve. The most common symptoms of HCC upon initial presentation include the following:

abdominal pain, weight loss, weakness, abdominal swelling (ascites) and jaundice. An additional 1-3% of patients initially present with symptoms related to metastatic disease, including body pain to the spine or hips. The most common signs of HCC are hepatomegaly, ascites, fever, splenomegaly, muscle wasting and jaundice. Laboratory values are non-specific and are often more related to the underlying liver disease than the HCC. However, many patients with HCC are asymptomatic at the time of diagnosis or have their tumors incidentally discovered on imaging done for unrelated reasons. The lack of symptoms highlights the importance of routine surveillance in patients with known cirrhosis.

Given that the vast majority of patients with HCC have underlying cirrhosis, the first manifestation of HCC can be hepatic decompensation, such as jaundice, hepatic encephalopathy, or ascites. In a patient with known cirrhosis a decline in a patient's hepatic function should heighten clinical suspicion for the development of HCC. However, a lack of known chronic liver disease and/or cirrhosis at presentation does not preclude the possibility of HCC. In many cases, patients were exposed to one of the inciting risk factors, such as HCV, decades earlier and have unrecognized chronic liver disease. In our experience, nearly 40% of patients had HCC as their first presentation of cirrhosis.

HCC Surveillance Tests

Ultrasound is the most widely used radiologic test for HCC surveillance [12]. It has several advantages including being non-invasive, cheap, and having no risk of contrast or radiation exposure. The efficacy of ultrasound in surveillance has been primarily evaluated in prospective cohort studies, as there have not been any randomized controlled trials assessing ultrasound in patients with cirrhosis. The sensitivity of ultrasound for the detection of early stage HCC ranged from 29% to 100% in these studies, whereas its specificity ranged from 94-100%[13]. In a recent meta-analysis, the pooled sensitivity of ultrasound for early stage HCC was only 63% (95% CI 49-76%) meaning that over one-third of all tumors were missed or diagnosed at advanced stages (Figure [13]). The authors also concluded that the level of evidence supporting ultrasound as a surveillance test is weak with significant limitations such as referral bias and verification bias.



Furthermore, all studies included in this meta-analysis were conducted in Europe and Japan so it is unclear if these results are generalizable to patients in the United States. In the Hepatitis C Antiviral

Long-term Treatment Against Cirrhosis (HALT-C) Trial, a large multicenter study in the United States, the sensitivity of ultrasound for early stage tumors was substantially lower [14]. Of 39 patients with HCC analyzed in a nested case-control study, only 14 were detected by ultrasound at an early stage. These results were confirmed in a large prospective single-center cohort study, in which the sensitivity of ultrasound for early stage HCC was only 31.7%.

Two possible etiologies that may limit ultrasound's effectiveness in clinical practice, as compared to its efficacy in clinical trials, are operator dependency and differences in patient characteristics. While well-trained technicians and/or physicians performed the ultrasounds in most clinical trials, radiology technicians with varied experience perform these scans in routine clinical practice [15]. This could easily impact the sensitivity of ultrasound, given its operator dependent nature. Alternatively, the sensitivity of ultrasound may be influenced by patient characteristics as is the case for breast density with mammography[16]. For HCC surveillance, the ability of ultrasound to accurately visualize the liver in patients with morbid obesity or a very nodular liver may be impaired [17].

Some studies have proposed that CT or MRI may be more sensitive as alternative imaging studies for the detection of HCC. A systematic review found the sensitivity of CT for HCC at any stage was 68% (95% CI 55-80%) and the sensitivity of MRI was 81% (95% CI 70-91%) [18]. Although these numbers are encouraging, it is important to note that CT and MRI have only been studied as diagnostic tests and not as surveillance tests with regards to early stage HCC in patients with cirrhosis. Additionally, the increased cost and potential adverse effects, such as radiation exposure, limit their utility in surveillance. There is currently insufficient evidence for the use of CT or MRI in routine clinical practice, and ultrasound remains the recommended radiologic test of choice until further studies have been performed.

Alpha feto-protein (AFP) is the best-studied serologic test for HCC surveillance. A level of 20 ng/mL has become the most commonly used cut-off to trigger further evaluation in clinical practice, although it is important to note that this value was derived from a study in which only one-third of patients had early stage HCC [19]. A systematic review of five studies evaluating AFP at this cut-off in patients with cirrhosis showed sensitivities ranging from 41-65% and specificities ranging from 80-94% for HCC at any stage [20]. A multicenter phase 2 biomarker study showed that AFP, using a lower cut-off of 10.9 ng/mL, had a sensitivity of 66% for early stage HCC [21].

AFP was included as an adjunct surveillance test, in addition to ultrasound, in the prior AASLD guidelines; however, it was removed from the most recent update published in 2010. This change has been very controversial and there has been extensive debate about its utility in clinical practice. The guidelines cited the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) study as the main source for the lack of efficacy of AFP in patients with cirrhosis; however, there are significant

limitations to this study[22]. First, only 40% of the patients had cirrhosis. Second, HCC surveillance was not the primary purpose of HALT-C. Third, AFP had a sensitivity of 61% at the time of HCC diagnosis, whereas US had a sensitivity of only 58%. Interestingly, an increasing AFP helped with the detection of 40% of patients with early-stage HCC in this study. Therefore, AFP appears to complement US for the surveillance of HCC.

In addition to ignoring the highest level of evidence for the efficacy of US combined with AFP in research studies, the HCC guidelines also neglect the effectiveness of the tests in clinical practice. In a study assessing the effectiveness of surveillance in a real world setting, ultrasound had a sensitivity of 44% and AFP had a sensitivity of 66%[23]. The sensitivity of surveillance was substantially increased to 90% when using the two tests in combination. There was a similar increase in sensitivity for early HCC from less than 50% for both tests to nearly 65% when the two were used in combination. There was not a significant trade-off in lost specificity when using the two tests in combination. In contrast to current guideline recommendation, these data suggests that ultrasound is insufficiently sensitive in isolation and that AFP should continue to be used.

There have also been other tumor biomarkers, including des-gamma carboxy-prothrombin (DCP) and the lens culinaris-agglutinin reactive fraction of AFP (APF-L3%), but there is insufficient evidence for their use in clinical practice currently [17]. In a nested case-control study among patients in the HALT-C trial, DCP and AFP had sensitivities of 74% and 61% respectively for HCC at any stage, which was increased to 91% by using the two markers in combination [24]. Another recent large multi-center study demonstrated that AFP, at a cut-off of 10.9 ng/mL, is more sensitive for early stage HCC than either of these two new biomarkers[21]. AFP-L3 only had a sensitivity of 37% (95% CI 31-45%) for early stage tumors and DCP had a sensitivity of 56% (95% CI 53-75%), whereas AFP had a sensitivity of 66% (95% CI 56-775). Further studies are necessary to better evaluate the potential role of AFP-L3 and DCP, but the use of these markers for HCC surveillance in clinical practice is not supported with currently available evidence.

HCC Surveillance Interval

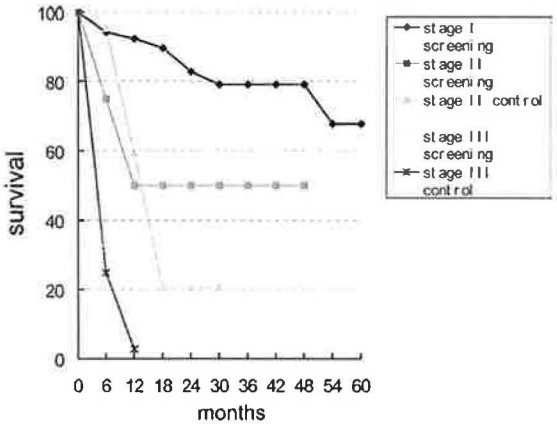
Although the ideal surveillance interval is not known, a screening interval of 6 months has been proposed on the basis of tumor doubling times [25]. A recent meta-analysis demonstrated a significantly higher sensitivity for early stage HCC with semi-annual versus annual surveillance[13]. Sensitivity was improved to 70% by performing surveillance every six months compared a sensitivity of 50% when surveillance was performed annually. A randomized controlled trial demonstrated that surveillance performed every three months does not further improve its effectiveness as compared to six-month intervals [26].

Impact of HCC Surveillance on Mortality

The most reliable method of evaluating the efficacy of ultrasound and AFP for HCC surveillance would be conducting a randomized controlled trial. There have been two large randomized controlled trials in China using ultrasound and AFP in patients with chronic HBV. In both trials, surveillance was conducted every 6 months and compared to patients who did not receive any routine screening.

The first study evaluated 17,920 carriers of HBV randomized to surveillance (n=8,109) or no surveillance (n=9,711) and then followed for an average of 14.4 months[27]. Among the patients randomized to the surveillance group, 38 patients developed HCC, of whom 29 (76.3%) were detected at early stages; in contrast, 18 patients developed HCC in the non-surveillance group and none of them were detected at an early stage ($p< 0.01$). A higher proportion of patients in the surveillance group met the criteria for surgical therapy, with 24 patients having surgical resection in the surveillance group compared to 0 patients in the non-screening group ($p< 0.05$). Accordingly, the 1-year and 2-year survival rates for the surveillance group were 88.1% and 77.5%, respectively, compared to a 0% survival rate at 1 year for the non-screening group. The authors acknowledged that this study was limited by lead-time bias, though it would theoretically account for only a survival difference of 5.4 months. Given that over three fourths of the surveillance population survived for 2 years, whereas no patients survived longer than 1 year in the non-screening group, the authors concluded that surveillance would reduce HCC-associated mortality rates.

The second randomized controlled trial evaluated 19,200 hepatitis B carriers who were randomized to surveillance (n=9,757) or no surveillance (n=9,443)[28]. A total of 86 patients developed HCC in the surveillance group, of whom 60% were early stage, compared to 67 patients who developed HCC in the non-surveillance group, of whom none were early stage. The mortality rate of patients undergoing surveillance was significantly lower than the control group (83.2 vs. 131.5 per 100,000; $p< 0.01$), with a hazard ratio of 0.63 (95% confidence interval, 0.41–0.98). These results demonstrate that the strategy of surveillance among patients with chronic HBV reduces overall mortality (Figure [28]).

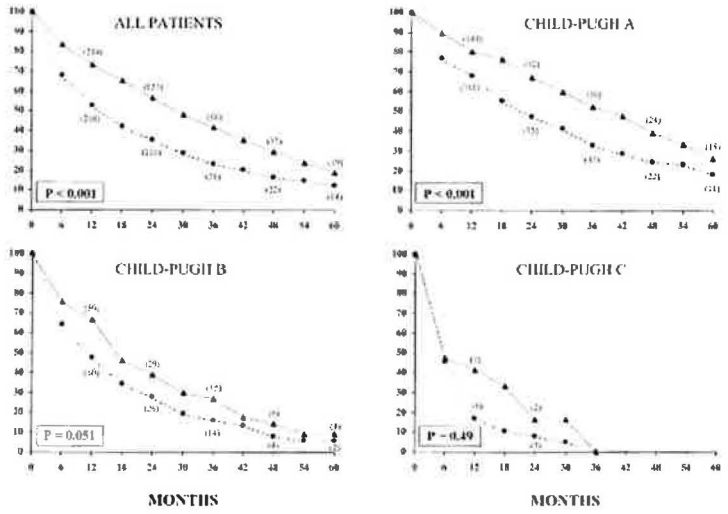


However, it is unclear whether all the patients in these two studies had the same risk of developing HCC, given the low rate of HCC development seen. These studies did not mention the number of patients who had cirrhosis or evidence of viral replication, and the studies most likely included patients who were asymptomatic carriers and are at a lower risk for developing HCC. Therefore, the results are not

generalizable to the majority of patients at risk for developing HCC.

Although randomized controlled trials have been performed in China in patients with chronic HBV, the results cannot be extrapolated to cirrhotic patients, who account for the majority of patients with HCC worldwide. The impact of surveillance on mortality in patients with cirrhosis has only been assessed in nonrandomized trials to date (i.e., a level II recommendation consisting of cohort or uncontrolled studies). Some studies have shown that patients undergoing surveillance with ultrasound and AFP have a better overall survival when compared to either historical controls or patients with HCC who did not undergo surveillance. The results of these studies are also fraught with lead-time and length-time biases that limit their generalizability of improvements in survival with surveillance.

In this prospective cohort study of 451 patients with cirrhosis and HCC, patients who underwent surveillance had a prolonged survival compared to those who had not undergone surveillance, after adjusting for lead-time bias[29]. The most substantial benefit was seen in patients with Childs A cirrhosis although patients with Childs B cirrhosis still derived a statistically significant survival benefit (Figure [29]). Given the competing risk of dying from liver related complications, there is likely not a benefit in performing HCC surveillance in patients with Childs C cirrhosis who are not otherwise transplant candidates.

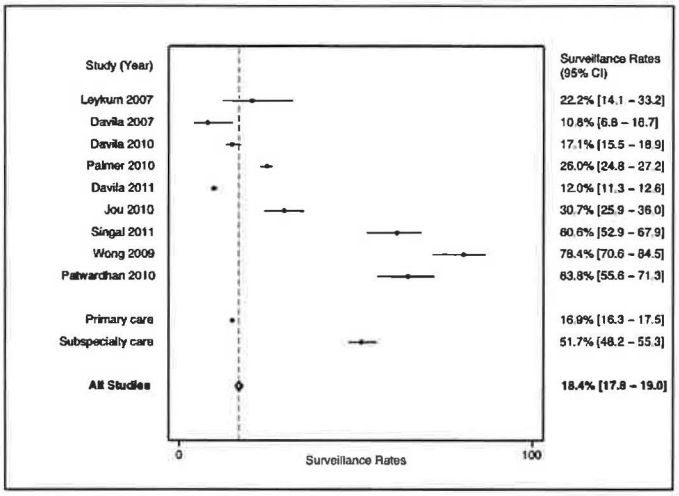


Cost Effectiveness

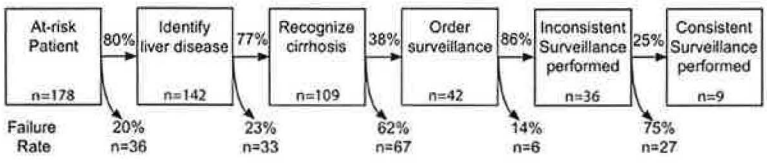
The standard threshold for cost effectiveness has been determined to be a maximal of $50,000 per quality-adjusted life year (QALY). Economic models studying the benefits of surveillance programs in HCC have been analyzed. Surveillance with biannual ultrasound and alpha-fetoprotein (AFP) in Child-Pugh class A cirrhotics increases the mean life expectancy with cost effectiveness ratios between $26,000 and $55,000 per QALY[30]. When a similar analysis was performed in patients with HCV cirrhosis, the cost-utility ratio was $26,689 per QALY[31]. Another study evaluating the cost effectiveness of biannual AFP and ultrasound in HCV Child-Pugh class A cirrhosis revealed a cost effectiveness ratio of $33,083 per QALY[32]. Therefore, screening with ultrasound and AFP has been demonstrated to be cost effective in patients with compensated cirrhosis.

Underutilization of HCC Surveillance

Although surveillance can be highly efficacious for detecting early HCC[33], its effectiveness in clinical practice may be impacted by low utilization rates among at-risk patients. Low HCC surveillance utilization rates were first reported by Leykum and colleagues[34] and have since been replicated in several studies, including three analyses from multi-center databases[35-37]. Most studies found surveillance rates below 30%, although rates of 60-80% were reported in single-center studies from tertiary care and/or community practices. Subspecialty care appears to be the strongest predictor of surveillance rates, with patients who received subspecialty care from gastroenterologists/ hepatologists having significantly higher surveillance rates than patients followed by primary care physicians (52% vs. 17%, p<0.001). Overall, a recent meta-analysis found a pooled surveillance rate of 18.4% (Figure [38]), which is substantially lower than rates seen in other cancers, such as colon, breast, and cervical cancer which now have screening rates near 60% throughout most of the United States[39].



Surveillance is a complex process in clinical practice, with multiple potential steps that are prone to failure[40]. Providers must accurately identify high-risk patients and order appropriate surveillance testing, the healthcare system must schedule the tests, and patients must adhere with surveillance recommendations[41]. A breakdown at any step results in surveillance failure. This challenge is particularly relevant in primary care settings, where providers face increasing time constraints and might be less knowledgeable about HCC guidelines[42]. We recently completed a retrospective cohort study to characterize reasons for lack of HCC surveillance among 178 patients with HCC at Parkland Hospital. We found multiple failure points in the surveillance process, including 40% of patients having unrecognized liver disease and/or cirrhosis prior to presenting with HCC (Figure [43]). This issue is consistent with a study by Stravitz and colleagues, in which 21.9% of patients presented with HCC without known cirrhosis[44]. However, we found that failure to order surveillance among patients with known cirrhosis was the most common reason

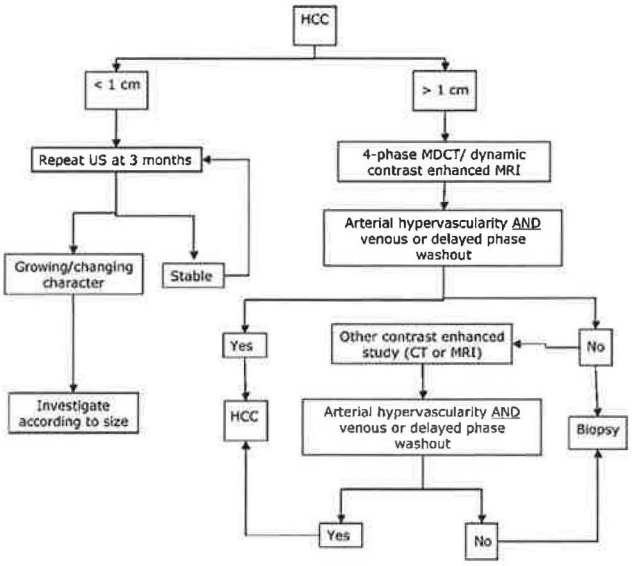


for lack of HCC surveillance. Further studies are necessary to determine if this failure to order HCC surveillance is related to provider knowledge regarding guidelines, attitudes regarding its effectiveness, or other barriers in clinical practice.

Diagnosis of HCC

The diagnostic algorithm for HCC is different from many other cancers in that it can often be diagnosed radiologically, without the need for biopsy. As discussed above, most HCC are initially detected by surveillance ultrasound or found incidentally done on imaging for other reasons (e.g. abdominal pain). After a lesion has been found, a 4-phase CT scan or MRI must be performed to make a diagnosis of HCC. The typical CT scan performed in the emergency room only has two phases – noncontrast and portal venous phase – and is insufficient to diagnose HCC.

In the arterial phase, an HCC nodule will enhance more intensely than the surrounding liver and then will enhance less strongly than the surrounding liver in the portal venous phase ("washout"). In the delayed phase, the presence of ''washout'' persists, and sometimes ''washout'' is only present in the delayed phase, highlighting the importance of having a delayed phase when evaluating for HCC. The presence of arterial uptake followed by washout is highly specific for HCC. Thus, to properly document the existence of HCC, a 4-phase study is required: unenhanced, arterial, venous and delayed phases. The imaging characteristics of HCC on CT/MRI are related to the dual blood supply of the liver. The liver receives most of its blood supply from the portal vein and a minority from the hepatic artery. Alternatively, HCC derive most of their blood supply from branches of the hepatic artery.



For lesions smaller than 1 cm, no detailed investigation is required because most of these will be cirrhotic nodules rather than HCC. However, close follow-up at 3-month intervals is recommended using the technique that first documented the presence of the nodules. If these were detected by screening ultrasound, then it is recommended that ultrasound should be the technique of follow-up.

For lesions above 1 cm in diameter, either dynamic MRI or multi-detector CT should be used. If the appearances are typical for HCC on either MRI or CT scan, then no further investigation is required and the diagnosis of HCC is confirmed. If the appearances are not typical for HCC (and do not suggest a

definite alternate diagnosis), then one of two strategies is possible. A second study (the other of CT scan or MRI) could be performed. If the appearances are typical on the second study, the diagnosis of HCC is confirmed. Alternatively, an atypical study could trigger a biopsy (Figure [7]).

If a biopsy is done, it should be interpreted by an experienced pathologist with the aid of markers staining for cytokeratins (CK7 and CK19), heat shock protein 70, hepar, glypican 3 and glutamine synthetase. Concerns over tumor seeding the biopsy tract or bleeding from a biopsy appear to be unfounded, as recent studies have not confirmed these historical concerns. If the biopsy is negative, the lesion should be followed with imaging every 3-6 months until the nodule changes in size or displays diagnostic imaging characteristics for HCC. If the lesion enlarges but remains atypical, a repeat biopsy is recommended at that time. There is currently no role for PET imaging in the diagnosis or staging of HCC.

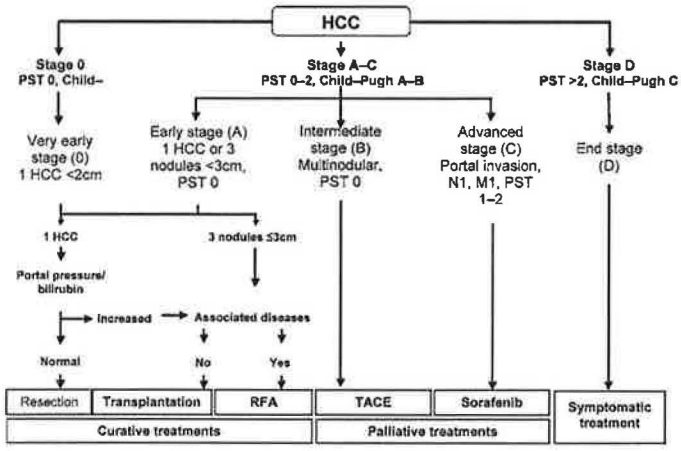
Staging Systems for HCC

There is a lack of consensus on the preferred staging system for HCC. Traditionally the TNM staging system is used to stage most other cancers. Although this system adequately stratifies patients into prognostic groups, it fails to consider the patients' underlying liver function or performance status. Similar concerns exist for the Okuda staging system, a conventional staging system initially derived among Asian HCC patients. Given that HCC typically occurs in the setting of cirrhosis, underlying liver function and/or performance status often limit our ability to treat patients and are important to take into account. The Cancer of the Liver Italian Program (CLIP), Japan Integrated Scoring System (JIS), and Barcelona Clinic Liver Cancer (BCLC) classification systems attempt to overcome the shortcomings of TNM staging by combining tumor-related parameters with underlying liver function and patient performance status (Table). The Japan Integrated Scoring System (JIS) has been used in Japan with better discriminatory power than TNM, although it still requires Western validation. The Cancer of the Liver Italian Program (CLIP) score has been validated in several centers in Europe but was associated with different survival rates when applied in Asian centers, compromising its external validation. Furthermore, neither of these systems has been linked to appropriate therapies for patients. The Barcelona Clinic Liver Cancer (BCLC) staging classification has been shown to have good discriminatory power, been externally validated, and has been linked to appropriate therapy. Therefore, this is currently the staging system endorsed by the AASLD and incorporated into guidelines.

TNM	Tumor number/size Lymph nodes Metastases		
Okuda	% Liver involvement	Albumin Bilirubin Ascites	
JIS	TNM	Child Pugh	
CLIP	% Liver involvement Portal vein invasion	Child Pugh AFP	
BCLC	Tumor stage	Child Pugh	Performance status

Treatment for HCC

This topic is beyond the scope of this talk but I want to highlight a couple important points. First, the effectiveness of HCC treatment depends upon the disease stage at the time of diagnosis. Although curative options are available for early HCC, the treatment of advanced HCC continues to be primarily palliative (Figure). For early-stage tumors (BCLC stage A), surgical resection has provided 5-year survival rates of 70% in carefully selected patients with preserved hepatic function, no evidence of portal hypertension, and single small asymptomatic tumors (<5 cm in maximal diameter). Liver transplantation is the preferred method of treatment for patients not amenable to surgical resection but only for those restricted to the Milan criteria (single nodule <5 cm or <3 nodules each <3 cm in diameter). The 5-year survival rate reported for liver transplantation is 74%.



Ablative treatments, specifically percutaneous ethanol injection and radiofrequency ablation, have demonstrated 5-year survival rates of 37% in BCLC stage A patients not amenable to resection or transplantation. It is estimated that approximately 30% of patients with HCC are currently diagnosed at early stages at which these therapies can be administered. These survival rates are in stark contrast to the average survival of less than one year reported for advanced HCC [45].

Second, patients who have Child C cirrhosis are typically not eligible for any therapies, outside of liver transplantation, and are typically only treated with best supportive care. Given that most patients at Parkland are not transplant candidates for a variety of reasons, most commonly lack of insurance, the benefit of performing surveillance in Child C patients is limited. Similarly, patients who have significant comorbid conditions and poor performance status do not benefit from surveillance given a lack of treatment options.

Finally, there are multiple different treatment options for HCC that must take into consideration not only tumor stage but also severity of the underlying liver disease and the patient performance status. Furthermore, the various treatments are all administered by different physicians, including hepatologists, surgeons, oncologists, and interventional radiologists. Given this complexity, HCC treatment is one area in which multidisciplinary care clinics have been shown to improve patient care and overall outcomes.

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