Surveillance for Hepatocellular Carcinoma

Epidemiology and Impact of HCC

Epidemiology

Worldwide, in 2020 hepatocellular carcinoma (HCC) is the seventh most common malignancy (Figure 1) and the second leading cause of cancer-related death (Figure 2).[1] In the United States, the National Cancer Institute (NCI) data for “liver cancer” combines liver and intrahepatic bile duct carcinoma.[2] The annual reported rate of liver cancer in the United States has changed significantly in the past 30 years—in 1992 the rate of new cases of liver and intrahepatic bile duct carcinoma was 4.46 per 100,000 persons, but this increased steadily to a peak of 9.38 cases per 100,000 persons in 2015, followed by a decrease in recent years (Figure 3).[2,3] In 2020, there was an estimated 42,810 new cases of liver and intrahepatic bile duct carcinoma reported in the United States.[4] The significant increase in incidence of HCC in the United States that occurred in the past 30 years has been largely attributable to HCV-related HCC.[5] Most of the cases of liver and intrahepatic bile duct carcinoma occurred in persons 55 to 74 years of age (Figure 4) and rates were the highest in persons who are American Indian/Alaska Natives or Hispanic (Figure 5).[2] Data from 2000 to 2017 showed overall an incidence rate of liver and intrahepatic bile duct carcinoma in the United States that is consistently higher in males than females (Figure 6).[2,6] For 2020, liver and bile duct cancer was the 13th leading cause of new cancer diagnoses in the United States, accounting for 2.4% of new cancer cases (Figure 7).[2] From 2014-2018 liver and intrahepatic bile duct cancer was the sixth leading cause of cancer death in the United States and the median age of those who died was 68 years.[2]

Risk Factors

Cirrhosis from any cause is the primary risk factor for HCC: approximately 80% of cases of HCC occur in individuals with cirrhosis and the risk of developing HCC increases with fibrosis stage.[7,8] The most common risk factors for developing HCC are chronic viral infection (with HCV or hepatitis B virus [HBV] or both), alcoholic liver disease, and, to a lesser extent, nonalcoholic fatty liver disease.[9,10] In the United States, approximately 30 to 50% of persons with HCC are infected with HCV.[11,12,13] Persons with chronic HCV infection and cirrhosis have a 1 to 4% annual risk of developing HCC.[14] The risk of developing HCC among persons with HCV increases with substantial alcohol intake—the risk increases in a linear fashion if daily alcohol intake is greater than 60 g (approximately 6 cans of beer, shots of liquor, or glasses of wine), for both men and women.[15] Diabetes has also been identified as a risk factor for HCV-associated HCC.[16] Less frequently cited risk factors for developing HCC include stage 4 primary biliary cirrhosis, hemochromatosis, glycogen storage disease, Wilson's disease, alpha-1-antitrypsin deficiency, and acute intermittent porphyria.[9,17,18]
Prognosis of Persons Diagnosed with HCC

The overall prognosis for persons diagnosed with HCC in the United States has improved in the past 15 years, but it remains poor, with an overall 5-year survival of approximately 20%.\cite{2,9,19} In general, persons who have HCC detected after the onset of symptoms have an even worse prognosis, with an overall 5-year relative survival less than 10%.\cite{2,8} Symptoms associated with HCC may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, watery diarrhea, and bone pain (from metastases). In contrast, detection of very early-stage HCC can be cured with an excellent long-term prognosis.\cite{9} Unfortunately, the vast majority of individuals diagnosed with HCC have cancer that is advanced beyond the stage where surgical cure with surgical resection or locoregional ablative therapy is an option.
Benefit of HCC Surveillance with HCV Infection

Rationale for HCC Surveillance

The rationale for conducting HCC surveillance is that regular screening of asymptomatic persons at risk for HCC may detect tumors at an early stage when potentially curative treatment can be offered.[8,9,20,21] Early detection with HCC is particularly important, given the very poor prognosis with lesions that are not detected early.[8,9,22]

Definition of Screening and Surveillance

By definition, screening a person for HCC means they have no symptoms related to HCC and the clinician does not have a reason to suspect the individual has HCC. With screening, the person is asymptomatic but undergoes testing in order to detect HCC early and before the development of symptoms.[20] Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident.[20] In addition, the term surveillance has been used to describe regular clinical monitoring in individuals who already have cancer. For the purposes of this topic review, we will refer to HCC surveillance as the activity of screening persons who do not have a known diagnosis of HCC.

Evidence Supporting Surveillance with Chronic Hepatitis

The main body of evidence to support HCC surveillance is a single cluster randomized controlled trial exists that assessed the impact of HCC surveillance on HCC-related mortality; this study enrolled 18,816 individuals aged 35 to 59 with HBV infection or a history of chronic hepatitis in urban Shanghai, China.[23] The investigators randomized 300 units (factories, businesses, schools) 1:1 to undergo HCC surveillance (with serum alpha-fetoprotein (AFP), with cutoff value 20 ng/mL, and ultrasound every 6 months) versus usual care.[23] Overall, approximately two-thirds of the individuals enrolled had documented positive HBsAg; infection with hepatitis C virus was not assessed.[23] The screening group had only a 58% compliance with screening, but notably had HCC diagnosed at an earlier stage (Figure 8) and had a reduction in HCC-related mortality when compared with the control group (Figure 9).[23] Since most of the persons in this study had chronic hepatitis B virus (HBV) infection, it is not the ideal study to support screening in persons with chronic HCV, but it is the largest prospective study of HCC screening in any population and provides evidence for screening in the hepatitis B population. There are also several observational trials and systematic reviews involving persons with cirrhosis that have shown surveillance for HCC was associated with earlier-stage tumor detection and improved survival.[24,25,26] Unfortunately, in addition to these data not being specific for HCV-associated cirrhosis, many of these studies had insufficient length of follow-up to assess survival, but did not adjust for liver disease severity or lead-time or selection bias.

Limited Data for HCC Surveillance with HCV Infection

There has been significant controversy about whether the findings of the trial conducted in China (that predominantly involved persons with chronic HBV infection) can be extrapolated to individuals with chronic HCV infection and serve as the basis to recommend HCC screening in persons with HCV infection. To date, there have been no published randomized, controlled trials that have evaluated HCC screening specifically in persons with chronic HCV infection and cirrhosis. This is likely to remain the case given the established role of HCC surveillance in routine clinical care in persons with cirrhosis. There have been a number of small observational studies of varying quality done in mixed populations, but these studies did not separate persons with chronic HCV infection from those with chronic HBV infection.[27]
Indications for HCC Surveillance

Indication for HCC Surveillance

In 2018, the American Association for the Study of Liver Diseases (AASLD) issued updated guidelines for the Treatment of Hepatocellular Carcinoma.[28] The 2018 AASLD HCC Guidelines recommend that all adults with cirrhosis of any etiology, should have surveillance for HCC because surveillance improves survival and increases the detection of early-stage HCC.[28] These guidelines, however, do not address HCC surveillance in persons with advanced fibrosis who do not have cirrhosis.[28] In addition, these guidelines, do not make specific recommendations for persons with chronic HCV or chronic hepatitis B virus (HBV) infection.[20,28] Other guidelines, however, recommend performing HCC surveillance in persons with chronic HCV infection who have developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4).[29] If a person has unknown cirrhosis status (or unknown stage of liver fibrosis), they should undergo evaluation of liver fibrosis stage, especially given the availability of improved noninvasive options for evaluating hepatic fibrosis.[30,31] For persons with chronic HCV and cirrhosis, achievement of sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy reduces the risk of HCC by 71 to 79%.[32] Although the risk of HCV-related HCC decreases following successful treatment and cure of HCV, the risk of HCC is not eliminated.[32,33,34,35,36] Accordingly, individuals with chronic HCV infection who are undergoing HCC surveillance should continue to do so, even if they achieve a sustained virologic response following treatment of HCV.[37]

Indications for HCC Surveillance in Persons with HBV and HCV Coinfection

Since a significant number of persons with chronic HCV also have coinfection with HBV, it is important to review current recommendations for HCC surveillance in persons with chronic HBV infection. In general, HBV has a significantly stronger oncogenic potential than HCV. In 2018, the AASLD issued the document Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance.[38] This document includes recommendations for HCC surveillance in persons with chronic HBV infection. Note these recommendations differ from the 2018 AASLD Hepatocellular Carcinoma Guidelines, which do not make specific HCC surveillance recommendations for persons with chronic HBV infection.[28] The 2018 AASLD HCC Guidelines recommends HCC surveillance for the following groups of HBsAg-positive persons:[38]

- All persons with cirrhosis
- Asian men 40 years of age or older
- Black men 40 years of age or older
- Asian women 50 years of age or older
- First-degree family member with a history of HCC
- Persons with hepatitis delta (HDV) virus
Surveillance Testing Methods

Biomarker Serologic Tests

- **Alpha Fetoprotein (AFP):** Alpha fetoprotein (AFP) is the most widely used biomarker for HCC surveillance, but this test has a sensitivity of only 47 to 64% and a specificity of 82 to 95% for detecting HCC among persons with HCV infection. The test clearly performs suboptimally compared with hepatic ultrasound for HCC surveillance.[39] The poor sensitivity results primarily from the lack of uniform secretion of AFP by all HCC tumors.[40] The less than optimal specificity occurs because AFP can often be elevated above the upper limit of normal in persons with advanced fibrotic liver disease but without HCC.[41] Some experts have suggested that AFP can be useful for the diagnosis of HCC if the level is elevated at a higher threshold, but very few individuals have markedly elevated AFP levels at screening, thereby reducing the sensitivity of this maker if a high threshold is used. As outlined, for multiple reasons, AFP is no longer recommended as a routine surveillance test.[20,29,37]

- **Des-gamma-Carboxy Prothrombin (DCP):** Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance.[42] The protein DCP is an abnormal prothrombin molecule that forms in malignant cells as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor; this prothrombin defect in malignant cells is similar to the deficit in vitamin K deficiency and DCP is also known as the Protein Induced by Vitamin K Absence (PIVKA).[43,44] Experience with DCP in Western countries, particularly the United States, remains limited. In a large study involving persons with chronic HCV infection and cirrhosis, investigators examined DCP, AFP, and the combination of DCP and AFP, but none of these strategies showed adequate sensitivity and specificity to justify the use of DCP (with or without AFP) as a routine surveillance test.[42]

Radiographic Imaging

- **Hepatic Ultrasound:** Hepatic ultrasound, when performed by an operator with expertise, has a sensitivity of 60 to 80% and specificity greater than 90% for overall detection of HCC at any stage.[8,45,46] The sensitivity for detecting early-stage HCC is significantly lower, in the range of 45 to 60%.[45,47,48] When using hepatic ultrasound for HCC surveillance in persons with cirrhosis, screening every 6 months increases the detection rate of very early hepatocellular carcinomas and reduces the number of advanced tumors when compared with screening every 12 months.[49] It does not appear that routine screening every 3 months with ultrasound provides a significant benefit over every 6-month screening.[50] The clinician’s order for the hepatic ultrasound should designate the purpose of the ultrasound as a screening test for HCC. The interpretation of ultrasound is operator-dependent and can be difficult in persons who are obese or have underlying cirrhosis, particularly those with nodular cirrhosis. If a nodule less than 1 cm is detected, the recommendation is to increase the frequency of surveillance to every 3 months; if the lesion remains unchanged for 2 years or longer, the surveillance frequency can return to every 6 months.[20] If a nodule larger than 1 cm is detected, further testing should be performed with either multiphasic computed tomography (CT) or a multiphasic magnetic resonance imaging (MRI).[20]

- **Computed Tomographic Abdominal Scan:** No current evidence exists for routine use of computed tomographic (CT) abdominal scanning as a routine surveillance test for HCC. For persons with a liver nodule greater than 1 cm detected on ultrasound, a 4-phase (unenhanced, arterial, venous, and delayed) contrast CT scan of the liver can be of diagnostic value.[20,28] During the arterial phase, HCC lesions enhance more intensely than the surrounding liver, but the opposite is observed during the venous and washout phases (where HCC lesions have little enhancement). The characteristic finding with HCC is presence of arterial hypervascularity (uptake) in the lesion followed by venous or delayed phase washout. The role of multiphasic CT scan in the diagnosis of HCC is particularly important since many experts rely on CT or magnetic resonance imaging (MRI) findings to establish the diagnosis, without the need for liver biopsy, if characteristic radiographic findings for HCC are present in a person at risk for HCC.
Liver Magnetic Resonance Imaging (MRI): Similar to recommendations for abdominal CT scanning, no current evidence exists that supports a recommendation to use a hepatic MRI as a routine surveillance test. For persons with a nodule greater than 1 cm detected on ultrasound, a contrast-enhanced multiphasic MRI is recommended as a diagnostic test.[20] This should be distinguished from the use of MRI as a screening test since current guidelines do not recommend MRI as a screening test.
Guidelines for HCC Surveillance

As described below, slight differences exist between various practice guidelines for HCC screening recommendations, but the general approach for HCC screening is similar.

2018 AASLD Hepatocellular Carcinoma Guidelines

The 2018 AASLD HCC Guidelines recommend screening all adults with cirrhosis every 6 months using abdominal ultrasound, with or without AFP. For adults with suspected HCC based on a screening test result, the guidelines recommend further evaluation with either a multiphasic computed tomography (CT) or multiphasic magnetic resonance imaging (MRI). These guidelines do not make a recommendation regarding persons with stage 3 fibrosis, a group in whom HCC has been shown to occur, nor do they make a specific recommendation for persons with chronic HCV infection. In contrast, in 2011, the AASLD pointed out that surveillance benefit for screening persons with stage 3 fibrosis is uncertain.

EASL–EORTC HCC Clinical Practice Guidelines

In 2012, the European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC) issued clinical practice guidelines on the management of hepatocellular carcinoma. For persons with chronic HCV, these guidelines recommend HCC surveillance if the patient has cirrhosis or advanced liver fibrosis (F3). In support of their decision to include persons with F3 fibrosis for routine HCC surveillance, these guidelines note the difficulty of detecting the transition from advanced fibrosis to cirrhosis, and they highlight data that HCC can occur in persons with chronic HCV and bridging fibrosis. The EASL/EORTC HCC guidelines recommend performing HCC surveillance with abdominal ultrasound every 6 months. These guidelines do not recommend including AFP for routine surveillance, given the suboptimal performance of this serum test.

Implementation of HCC Screening

In the United States, several potential barriers exist for effective HCC screening in persons with chronic HCV infection have been identified, including unknown fibrosis stage of the individual, lack of clinician awareness of HCC screening guidelines, scheduling logistics, and cost of surveillance. Since current guidelines for persons with chronic HCV recommend HCC screening only for those with cirrhosis or advanced fibrosis, clinicians must first accurately identify which individuals meet these criteria. In one study of the implementation of HCC screening in the VA system that was conducted between 1998 and 2005, investigators identified 126,670 persons with HCV infection and 10.1% of these individuals had cirrhosis; among those with cirrhosis (with at least 2 years of follow-up), routine HCC surveillance occurred in 12.0%, inconsistent surveillance in 58.5%, and no surveillance in 29.5%. A contemporary assessment of HCC screening practice in the DAA era has not yet been done, but it would clearly need to account for the growing population of individuals who have cleared their HCV yet still have cirrhosis and who are aging with their liver disease.
Summary Points

- Cirrhosis (Metavir stage F4 fibrosis) is the most important risk factor for developing HCC in persons with chronic HCV infection. Less commonly, HCC will occur in persons who have advanced fibrosis (Metavir stage F3) but without cirrhosis.
- In the United States, the incidence of HCC has steadily increased and this rise is primarily attributed to the expanding prevalence of HCV-related liver disease and aging of the population living with chronic HCV.
- Persons who develop HCC have a poor prognosis with an estimated median 5-year survival duration of approximately 20%.
- Potentially curative therapies for early stage HCC include locoregional ablative therapy, hepatic resection or liver transplantation. The primary goal of HCC surveillance is to detect disease in an early stage and therefore increase the likelihood of potentially curative therapy.
- The 2018 AASLD HCC Guidelines recommend screening for HCC in all adults with cirrhosis using every 6-month abdominal ultrasound, with or without concomitant AFP screening. It is important to note that AFP sensitivity and specificity are both low and therefore AFP should not be used as a solitary screening tool.
- In persons with advanced fibrosis or cirrhosis, successful HCV treatment with DAA therapy can lower HCC risk by 71 to 79%.
- Despite the greatly reduced HCC risk from an SVR, the risk is not eliminated and clinicians should not stop HCC screening in persons after SVR is achieved. In persons who qualify for HCC screening, the standard recommended should continue on the same schedule after SVR is achieved and this message should be emphasized to these individuals.
Citations

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Figures

Figure 1 2020 Global Cancer Incidence Estimates

This graphic shows estimates for the number of global cases of cancer, by type of cancer in 2020. Globally, an estimated 905,677 persons had a diagnosis of liver cancer in 2020.

Figure 2 2020 Global Cancer Death Estimates

This graphic shows estimates for the number of global cancer-related deaths, by type of cancer in 2020. Globally, an estimated 830,180 persons died of liver cancer in 2020.

Figure 3 Rate of New Cases and Death Rate for Liver and Intrahepatic Bile Duct Cancer, United States, 1992-2017

These data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 21 Program (SEER21).

Figure 4 Incidence of New Liver and Intrahepatic Bile Duct Cancer in the United States, by Age Group, 2013-2017

As shown, in the United States, the most new diagnoses of liver cancer occur in persons 55 to 64 years of age. Note that for these statistics, liver cancer includes liver and intrahepatic bile duct cancer. These data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 21 Program (SEER21).

**Figure 5 Rates of New Liver Cancer in United States, by Race/Ethnicity and Sex, 2013-2017**

Data shown are the rate of new cases per 100,000 persons by race/ethnicity and sex for liver and intrahepatic bile cancers in the United States.


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<tr>
<td>Non-Hispanic</td>
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**Figure 6 Rates of New Liver Cancer in United States, by and Sex, 2000-2017**

Data shown are the rate of new cases per 100,000 persons by sex for liver and intrahepatic bile cancers in the United States.

**Figure 7 New Cancer Cases in United States**

Abbreviations: NOS = not otherwise specified
This graphic shows that liver cancer and intrahepatic bile duct cancer accounted for only 2.4% of the estimated new cancer cases in the United States in 2020.

Figure 8 Impact of Screening on Stage of HCC at Time of Diagnosis

In a trial performed in Shanghai, China, more than 18,000 persons with chronic viral hepatitis (most of whom had chronic hepatitis B), were randomized to screening for HCC or no screening (control). As shown, individuals who received screening were more likely to have their HCC diagnosed at an earlier stage (Stage 1) than those who did not have screening.

Figure 9 Impact of Screening on Survival after Diagnosis of HCC

In this trial, patients with chronic viral hepatitis who underwent screening for HCC had improved survival after the diagnosis of HCC when compared with the control group that did not receive screening for HCC.