Surveillance for Hepatocellular Carcinoma

Epidemiology and Impact of HCC

Epidemiology

Worldwide, hepatocellular carcinoma (HCC) is the sixth most common malignancy (Figure 1) and the second leading cause of cancer-related death (Figure 2). [1] Approximately 85% of global HCC cases occur in developing countries. [2] In the United States, until the rise in hepatitis C virus (HCV) cases occurred, HCC was relatively uncommon. However, the incidence of HCC in the United States radically changed in the past 40 years: in 1973 the HCC incidence was 1.51 cases per 100,000 persons, but this increased to 6.20 cases per 100,000 persons in 2011. [3] In 2012, there was an estimated 24,696 new cases of HCC diagnosed (Figure 3). [4] The rapid rise in incidence of HCC in the United States has been largely attributable to hepatitis C-related HCC. [5] More recent data are available from Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI), but these reports for "liver cancer" combine liver cancer and intrahepatic bile duct carcinoma. [6] In the United States, the CDC/NCI data reported 31,411 cases of combined liver cancer and intrahepatic bile duct cancer in 2014. [6] Most of the cases occurred in persons 50 to 80 years of age (Figure 4) and most involved whites (Figure 5). [6] Data from 2001 to 2006 showed overall incidence rate of HCC is approximately three times higher in males than females (Figure 6). [7] Among the 31,411 cases of liver and intrahepatic bile duct cancer reported in the United States in 2014, 72%) were males. [4] For the CDC/NCI data, in 2014, liver and bile duct cancer was the eighth leading cause of cancer-related death in the United States (Figure 7). [6]

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. [8, 9] 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. [10, 11] In the United States, approximately 30 to 50% of persons with HCC are infected with HCV. [2, 12, 13] Patients with chronic HCV infection and cirrhosis have a 1 to 4% annual risk of developing HCC. [14] The risk of developing HCC among persons infected with HCV increases with substantial alcohol intake—the risk increases in a linear fashion with daily alcohol intake greater than 60 g (approximately 6 cans of beer, shots of liquor, or glasses of wine), for both men and women. [15] 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. [10, 16, 17]

Prognosis of Patients Diagnosed with HCC
The overall prognosis for patients diagnosed with HCC in the United States has improved some in the past 15 years, but it remains poor, with an overall 5-year survival of approximately 12%.\textsuperscript{[10, 18, 19]} In general, patients who have HCC detected after the onset of symptoms have an extremely poor prognosis, with an overall 5-year survival of 0 to 10%.\textsuperscript{[9, 10]} Symptoms 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.\textsuperscript{[10]} Unfortunately, the vast majority of patients with HCC have cancer that is advanced beyond the stage where surgical cure 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 patients at risk for HCC may detect tumors at an early stage when potentially curative treatment can be offered.[9,10,20,21] Early detection with HCC is particularly important, given the very poor prognosis with lesions that are not detected early.[9,10,22]

Definition of Screening and Surveillance

By definition, screening a patient for HCC means that the patient has no symptoms and the clinician does not have a reason to suspect the patient has HCC. With screening, the patient 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]

Evidence Supporting Surveillance with Chronic Hepatitis

A single prospective 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 and the investigators compared patients who underwent HCC surveillance with those who did not undergo HCC surveillance.[23] Overall, approximately two-thirds of the patients enrolled had documented positive HBsAg and the screening group (n = 9,373) was offered every 6-month surveillance with abdominal ultrasound and alpha fetoprotein (AFP) and the control group received no surveillance (n = 9,443).[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 patients in this study had chronic hepatitis B, it is not the ideal study to support screening in patients with hepatitis C, 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 reviews involving patients with cirrhosis that have shown surveillance for HCC was associated with earlier-stage tumor detection and improved survival.[24,25,26] These data were not specific to HCV-related cirrhosis.

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 in persons living in the United States with chronic HCV infection and 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

In 2018, the American Association for the Study of Liver Diseases (AASLD) issued updated guidelines for the Treatment of Hepatocellular Carcinoma.[28] These 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] The Hepatocellular Carcinoma Guidelines, however, do not address HCC surveillance in persons with advanced fibrosis who do not have cirrhosis.[28] In addition, these guidelines, unlike prior versions, do not make special recommendations for persons with chronic HCV or chronic hepatitis B virus (HBV) infection.[20,28] Other guidelines, however, recommend performing HCC surveillance in patients with chronic HCV infection who have developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4).[29,30] If a patient 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.[31,32] 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 79%.[33] Although the risk of HCV-related HCC decreases following successful treatment and cure of HCV, the risk of HCC is not eliminated.[33,34,35,36,37] 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.[30]

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 and rates of HCC in patients with chronic HBV infection are higher than in persons with chronic HCV infection than with chronic HCV infection. 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 Hepatitis B Guidance recommends HCC surveillance for all of the following groups of HBsAg-positive patients:[38]

- All patients 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 D 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 inferior to hepatic ultrasound for HCC surveillance.[39] The poor sensitivity primarily results from the lack of uniform secretion of AFP by HCC tumors and the less than optimal specificity occurs because AFP is often elevated above the upper limit of normal in patients with advanced fibrotic liver disease but without HCC. Some experts have suggested that AFP can be useful for the diagnosis of HCC if the level is extremely elevated, but very few patients have extremely elevated AFP levels at screening. As outlined, for multiple reasons, AFP is no longer recommended as a routine surveillance test.[20,29,30]

- **Des-gamma-Carboxy Prothrombin (DCP)**: Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance.[40] 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).[41,42] 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 as a routine surveillance test.[40]

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.[9,43,44] The sensitivity for detecting early-stage HCC is significantly lower, in the range of 45 to 60%.[43,45,46] 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.[47] It does not appear that routine screening every 3 months with ultrasound provides a significant benefit over every 6-month screening.[48] 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 in size for 2 year 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 patients who have 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.

- **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 patients who have 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 different practice guideline recommendations for HCC screening, but the overall general approach for HCC screening is similar in each.

**2018 AASLD Hepatocellular Carcinoma Guidelines**

The revised published 2018 AASLD Hepatocellular Carcinoma Guidelines recommend screening all adults with cirrhosis every 6 months using abdominal ultrasound, with or without AFP.\[28\] 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).\[28\] These guidelines do not make a recommendation regarding patients with stage 3 fibrosis and they do not make a specific recommendation for persons with chronic HCV infection.\[28\] In contrast, in 2011, the AASLD pointed out that surveillance benefit for screening patients with stage 3 fibrosis is uncertain.

**AASLD/IDSA Hepatitis C Guidance**

The online American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) Hepatitis C Guidance recommends surveillance for HCC in persons with chronic HCV infection who have cirrhosis (Metavir stage F4) or advanced fibrosis (Metavir stage F3).\[30\] The recommended surveillance test is hepatic ultrasound and the recommended surveillance interval is every 6 months.\[30\] The AASLD/IDSA guidance recommends that HCC surveillance in persons with advanced fibrosis or cirrhosis should continue after treatment for HCV, even if a sustained virologic response (SVR) is achieved.\[30\] The AASLD/IDSA guidelines do not recommend using AFP as a surveillance test, but the AASLD/IDSA Hepatitis C Guidance has not been updated since the publication of the 2018 Hepatocellular Guidelines (which include AFP as optional in surveillance).\[30\]

**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.\[29\] For patients with chronic HCV, these guidelines recommend HCC surveillance if the patient has cirrhosis or advanced liver fibrosis (F3).\[29\] These guidelines include patients with advanced fibrosis based on the difficulty of detecting the transition from advanced fibrosis to cirrhosis; in addition, there are data that HCC can occur in patients with chronic HCV and bridging fibrosis. The EASL/EORTC HCC guidelines recommend performing HCC surveillance with abdominal ultrasound every 6 months.\[29\]

**Implementation of HCC Screening**

In the United States, several potential barriers exist for effective HCC screening in patients with chronic hepatitis C infection have been identified, including unknown fibrosis stage of the patient, lack of clinician awareness of HCC screening guidelines, scheduling logistics, and cost of surveillance.\[49,50,51\] Since current guidelines for patients with chronic hepatitis C recommend HCC screening only for those with cirrhosis or advanced fibrosis, clinicians must first accurately identify which patients meet these criteria. One study of the implementation of HCC screening in the VA system found that between 1998 and 2005, 126,670 patients with hepatitis C infection were identified and 10.1% of these patients had cirrhosis; among the patients 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%.\[27\]
Summary Points

- Cirrhosis is the most important risk factor for developing HCC in persons with chronic HCV infection. Less commonly, HCC will occur in patients who have advanced fibrosis but without cirrhosis.
- Previously, HCC was a rare malignancy in the United States, but now is the fastest growing cause of cancer-related death; the rise in the incidence of HCC is attributed to the high prevalence of HCV and aging of the population living with chronic HCV-infection.
- Patients who develop HCC have a poor prognosis with an estimated median survival duration of 4.3 to 20 months after diagnosis.
- Potentially curative therapies for early stage HCC include 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.
- Current published AASLD Hepatocellular Carcinoma 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.
- The online AASLD-IDSA Hepatitis C Guidance recommends surveillance for HCC using abdominal ultrasound every 6 months for all persons with chronic HCV who have cirrhosis (Metavir stage F4) or advanced fibrosis (Metavir stage F3). These recommendations are based on retrospective data and one prospective trial that primarily involved persons with chronic hepatitis B infection.
- In persons with advanced fibrosis or cirrhosis, successful HCV treatment with DAA therapy lowers HCC risk by 71%.
- Despite the greatly reduced HCC risk from an SVR, the risk is not eliminated and clinicians should not stop HCC screening in patients after SVR is achieved. In patients who qualify for HCC screening, the screening should continue on the same schedule after SVR is achieved and this message should be emphasized to patients.
Citations

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Figures

Figure 1 2012 Global Cancer Incidence Estimates

Abbreviations: NHL = non-Hodgkin's lymphoma
This graphic shows the global incidence estimates for the 10 most common cancers in 2012. Overall, an estimated 12.7 million new cancers occurred globally in the year 2008. Globally, approximately 780,000 persons had a diagnosis of HCC in 2012.

Figure 2 2012 Global Cancer Death Estimates

This graphic shows estimates for the number of global cancer-related deaths, by type of cancer in 2012. Globally, approximately 745,000 persons died of HCC in 2008.

Figure 3 Incident HCC in United States, 2000-2012

This graphic shows a steady increase in the number of new cases of hepatocellular carcinoma in the United States—from 11,469 cases in 2000 to 24,696 cases in 2012.

Figure 4 Incidence of New Liver Cancer Diagnosis in United States, by Age Group, 2014

As shown, the most new diagnoses of liver cancer occur in persons 50 to 80 years of age. Note that for these statistics, liver cancer includes HCC and intrahepatic bile duct cancer.

Figure 5 Incidence of New Liver Cancer Diagnosis in United States, by Race/Ethnicity, 2014

Note that for these statistics, liver cancer includes HCC and intrahepatic bile duct cancer.

Figure 6 Incidence Rates of HCC in United States, by Sex, 2001-2006

These data show the annual HCC incidence rates (per 100,000 persons) based on year of diagnosis. The incidence rates in males (green line) was approximately 3 times that in females (purple line).

Figure 7 Cancer-Related Death Rates in United States, 2014

Abbreviations: NOS = not otherwise specified
This graphic shows the cancer-related deaths in the United States. Note that for these statistics, liver cancer includes HCC and intrahepatic bile duct cancer.

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.