

Surveillance for Hepatocellular Carcinoma

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Module 2: [Evaluation, Staging, and Monitoring of Chronic Hepatitis C](#)
Lesson 6: [Surveillance for Hepatocellular Carcinoma](#)

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Significance of HCC and Rationale for Surveillance

Impact of Hepatocellular Cancer: Worldwide, hepatocellular carcinoma (HCC) is the sixth most common malignancy ([Figure 1](#)) and the third most common cause of cancer-related death ([Figure 2](#)). In the United States, HCC is the fastest growing cause of cancer-related death. The incidence of HCC in the United States has increased in recent years ([Figure 3](#)), largely attributable to a significant rise in hepatitis C-related HCC. In the United States, it is estimated that in 2013 there will be 30,640 new cases diagnosed and 21,670 deaths due to hepatitis C-related HCC.

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. Chronic HCV and chronic hepatitis B virus (HBV) infection are the most common risk factors for HCC. In the United States, approximately 50 to 60% of persons with HCC are infected with hepatitis C. Patients with chronic hepatitis C and cirrhosis have a 2 to 5% annual risk and a 7% to 14% risk over 5 years of developing HCC. 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). The overall incidence rate of HCC is approximately three times higher in males than females ([Figure 4](#)). Any patient with cirrhosis can develop HCC, including patients with cirrhosis from non-viral causes, such as alcoholic cirrhosis, autoimmune hepatitis, non-alcoholic fatty liver disease, hemochromatosis, glycogen storage disease, Wilson's disease, alpha-1-antitrypsin deficiency, and porphyria cutanea tarda.

Prognosis: The overall prognosis for patients diagnosed with HCC in the United States is poor, with an estimated median survival of 4.3 to 20 months and a 5-year survival of 10 to 15%. 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%. Symptoms may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, watery diarrhea, and bone pain (from metastases). A select group of patients with good performance status who have HCC diagnosed at an early stage have a predicted survival longer than 5 years, but unfortunately most patients with HCC have advanced stages of cancer at the time of diagnosis.

Rationale for HCC Surveillance: The rationale for conducting HCC surveillance is that regular screening of at-risk asymptomatic patients may detect tumors at an early stage when potentially curative treatment can be offered.

Evidence for the Benefit of HCC Surveillance in HCV-Infected Patients

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. Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident.

Evidence Supporting Surveillance in Patients 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. Overall, approximately two-thirds of the patients enrolled had documented positive HBsAg. 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). The screening group had only a 58% compliance with screening, but had their HCC diagnosed at an earlier stage ([Figure 5](#)) and had a reduction in HCC-related mortality when compared with the control group ([Figure 6](#)). 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.

Absence of Data for HCC Surveillance in HCV-Infected Patients: There has been significant controversy about whether the findings of the trial conducted in China that predominantly involved HBV-infected patients can be extrapolated to patients with hepatitis C infection, and if so, whether it is strong enough evidence to be the basis for recommending that screening be performed in HCV patients in the United States. To date, no prospective randomized controlled trials of HCC screening in HCV-infected patients living in the United States have been published. There have been a number of small observational studies of varying quality done in mixed populations, but these studies did not separate HCV-infected patients from HBV-infected patients.

Indications for HCC Surveillance in Patients with Hepatitis C

Indication for HCC Surveillance: For patients with chronic hepatitis C infection, expert guidelines recommend performing HCC surveillance in any patient with chronic hepatitis C who has developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4). Surveillance for HCC is not recommended for HCV-infected patients who do not have advanced fibrosis or cirrhosis. There are no clear-cut recommendations for patients with unknown stage of liver fibrosis. In this situation, some experts have suggested use of non-invasive markers to identify patients with probable advanced fibrosis or cirrhosis. Although the risk of HCV-related HCC decreases substantially in patients with cirrhosis who obtain a sustained virologic response with therapy for hepatitis C, the risk of HCC is not eliminated, even if they have documented improvement in cirrhosis.

Recommended Surveillance Interval for Screening: The interval time for surveillance is based on tumor doubling time, which generally is considered to occur in 6 to 12 months. Expert guidelines recommend using a surveillance interval of 6 months.

Indications for HCC Surveillance if Coinfected with Chronic Hepatitis B: Recommendations for HCC surveillance for patients with chronic hepatitis B are more aggressive than with hepatitis C. In general, hepatitis B is a much more oncogenic virus than hepatitis C, rates of HCC in hepatitis B patients are higher than hepatitis C patients, and HCC occurs in some patients with hepatitis B who do not have cirrhosis. For HCV-infected patients who are coinfecting with hepatitis B, the HCC surveillance recommendations issued by the American Association for the Study of Liver Disease (AASLD) for chronic hepatitis B should be followed. For patients with hepatitis B infection, any of the following are considered indications for HCC screening:

- Asian males 40 years of age or older
- Asian females 50 years of age or older
- Patients with cirrhosis
- Family history of HCC
- Africans older than 20 years of age

Implementation of HCC Screening: Given the large population with chronic hepatitis C infection in the United States, several potential barriers exist for effective HCC screening in patients with chronic hepatitis C infection, including lack of clinician awareness of HCC screening recommendations, difficulty in identifying the correct patient population for screening, and cost of surveillance. 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. Determining whether the patient has cirrhosis is a complex process and also requires education and training. 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%.

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 HCV-infected patients. 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 liver disease but without HCC. For example, a study that examined patients over a period of 13 to 14 years found that approximately 90% of AFP elevations were not associated with cancer. Instead, most cases involved a transiently elevated AFP level; for patients followed over this period, approximately 15% had an elevated AFP level at some point. 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. If there is uncertainty about an imaging study and a biopsy cannot be performed, then AFP might provide useful additional information.
- **Des-gamma-Carboxy Prothrombin (DCP):** Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance. The protein DCP is an abnormal prothrombin molecule generated as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant cells; 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). Experience with DCP in western countries, particularly the United States, remains limited. In a large study involving HCV-infected patients with cirrhosis, investigators examined DCP, AFP, and the combination of DCP and AFP, but none of these strategies showed adequate sensitivity to justify the use of DCP as a routine surveillance test. In contrast, DCP may have some utility as a marker of advanced HCC.

Radiographic Imaging

- **Hepatic Ultrasound:** Hepatic ultrasound is reported to have a sensitivity of 65 to 80% and specificity 87 to 94% for detecting HCC. The clinician's order for the hepatic ultrasound should designate the purpose of screening for HCC and the test should focus on examination of the right upper quadrant region, including evaluation of the liver for any evidence of a hepatic mass. 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.
- **Computed Tomographic Abdominal Scan:** No current evidence exists for routine use of computed tomographic (CT) abdominal scanning as a routine surveillance test for HCC. In contrast, for patients who have a liver nodule greater than 1 cm detected on ultrasound, many experts recommend using a 4-phase (unenhanced, arterial, venous, and delayed) dynamic contrast CT scan of the liver as a secondary test for diagnosis. 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 4-phase 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 hepatic MRI as a routine surveillance test. For patients who have a nodule greater than 1 cm detected on ultrasound, a dynamic contrast-enhanced MRI is often recommended as a secondary test. This should be distinguished from the use of MRI as a screening test since current guidelines

do not recommend MRI as a screening test.

Recommendations from Professional Organizations for HCC Surveillance

American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA): The recent AASLD/IDSA hepatitis C guidance recommends surveillance for HCC in persons with chronic HCV infection who have advanced fibrosis or cirrhosis (Metavir stage F3 or F4). The recommended surveillance test is hepatic ultrasound and the recommended surveillance interval is every 6 months. The AASLD/IDSA guidance recommends that HCC surveillance in HCV-infected patients with advanced fibrosis or cirrhosis should continue after patients receive therapy for HCV, even if they achieve an SVR. The AASLD/IDSA guidelines do not recommend using AFP as a surveillance test; evolving data have shown that AFP has poor sensitivity and specificity as a surveillance tool for HCC. In an earlier document, the AASLD provided an algorithm for investigating a liver nodule if found on hepatic ultrasound ([Figure 7](#)).

Institute of Medicine: In January 2010, the Institute of Medicine issued a report on Hepatitis and Liver Cancer, calling for increased attention to the problem of liver cancer as a potential consequence of chronic viral hepatitis and need for increased awareness, screening, and appropriate surveillance to be performed.

National Cancer Institute (at the National Institutes of Health): The National Cancer Institute states that based on fair evidence, screening for HCC would not result in a decrease in mortality from hepatocellular cancer. Further they state that screening for HCC could result in rare but serious side effects that could occur with needle aspiration cytology.

Summary Points

- Cirrhosis is the most important risk factor for developing HCC in patients with chronic hepatitis C 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 chronically HCV-infected population.
- 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.
- The AASLD practice guidelines recommend surveillance for HCC using abdominal ultrasound every 6 months for all HCV-infected patients who have advanced fibrosis or cirrhosis (Metavir stage F3 or F4). These recommendations are based on retrospective data and one prospective trial that primarily involved persons with chronic hepatitis B infection.
- In patients with advanced fibrosis or cirrhosis, successful treatment of HCV lowers the risk of developing HCC, but this risk is not eliminated. Accordingly, surveillance for HCC in patients with advanced fibrosis or cirrhosis should continue even after they achieve an SVR.
- Prior practice guidelines recommended using AFP in addition to ultrasound for HCC screening, but data showing low specificity and sensitivity of AFP has led to the AASLD recommendation to ultrasound alone.

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Figures

Figure 1 2008 Global Cancer Incidence

This graphic shows the global incidence of the most common cancers in in 2008. Overall, an estimated 12.7 million new cancers occurred globally in the year 2008. Approximately 750,000 persons had a diagnosis of HCC in 2008.

Source: International Agency for Research on Cancer. World Cancer Fact Sheet. August, 2010.

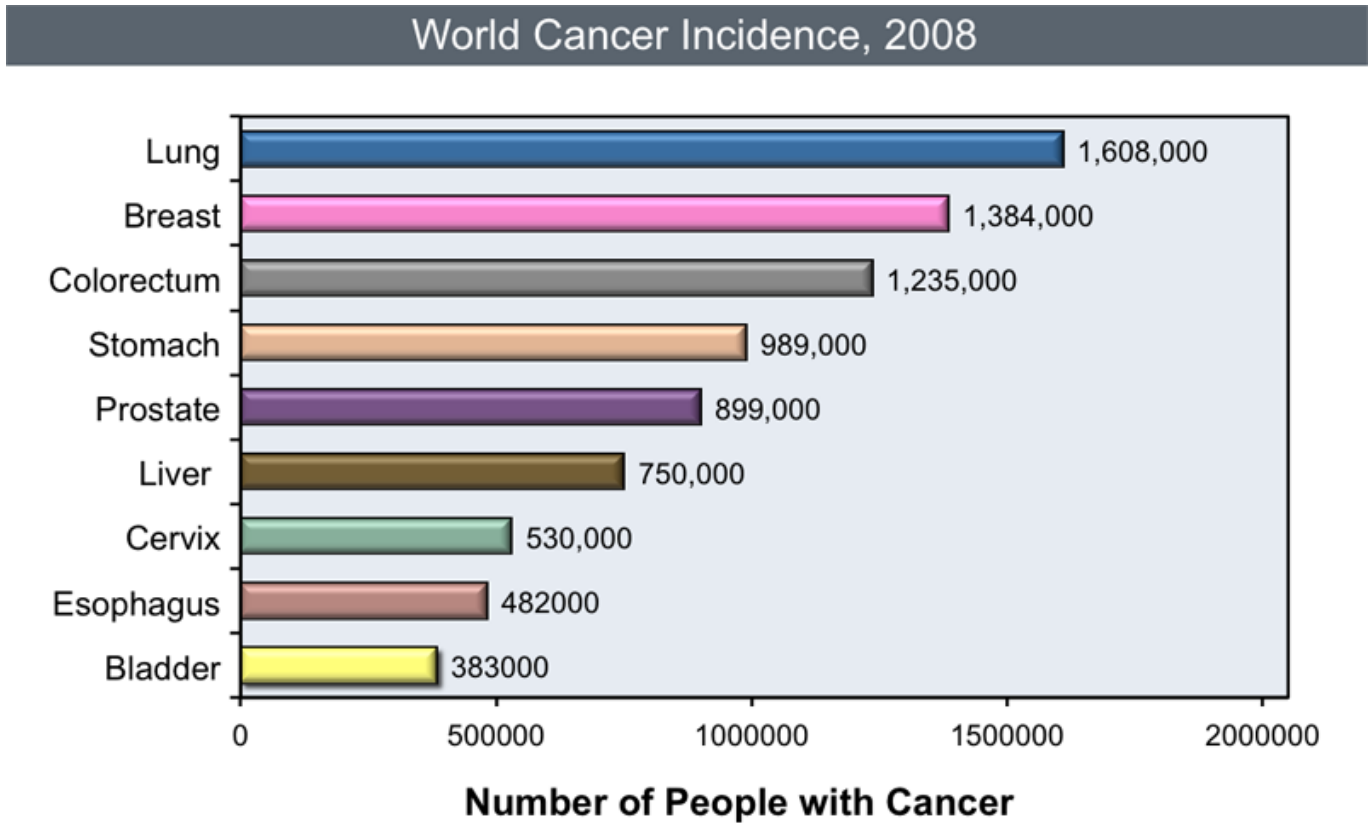


Figure 2 2008 Global Cancer Deaths

This graphic shows the number of global cancer deaths, by type of cancer in 2008. Approximately 700,000 persons died of HCC in 2008.

Source: World Health Organization. January 2013.

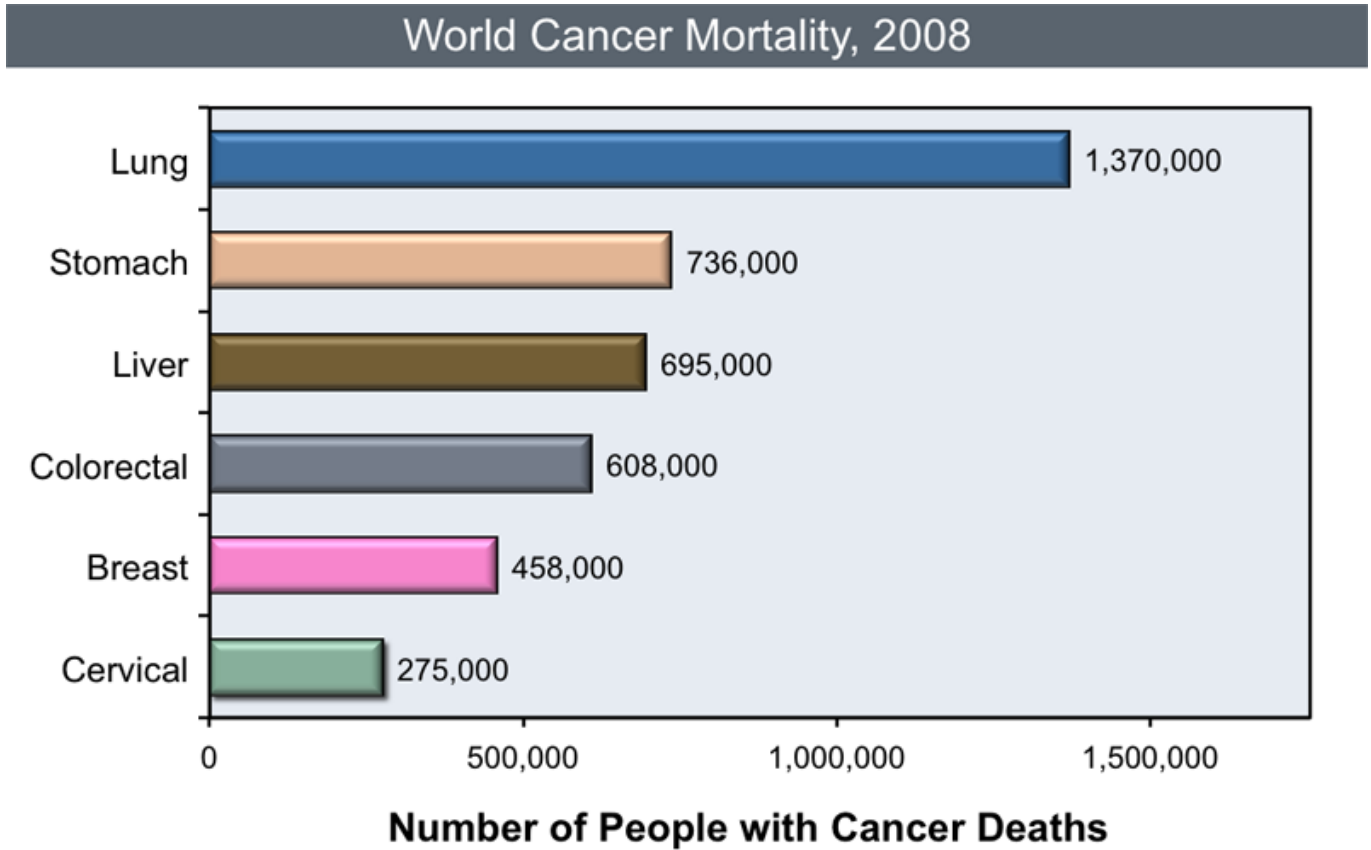


Figure 3 Age-Adjusted Rates of HCC in United States, 1992-2005

From 1992-2005, the age-adjusted rates of HCC have steadily increased, primarily due to increases in hepatitis C-related HCC.

Source: Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol.* 2009;27:1485-91.

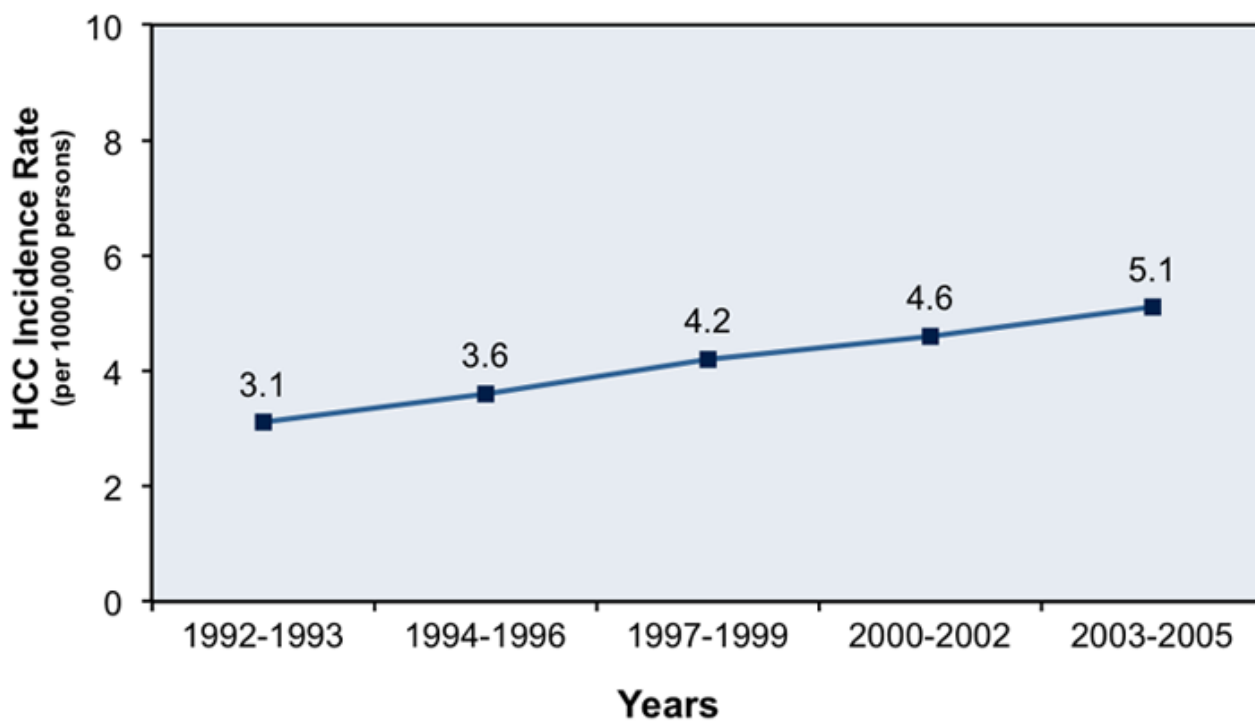


Figure 4 Incidence Rates of HCC in United States, by Sex, 2001-2006

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).

Source: Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma - United States, 2001-2006. MMWR Morb Mortal Wkly Rep. 2010;59:517-20.

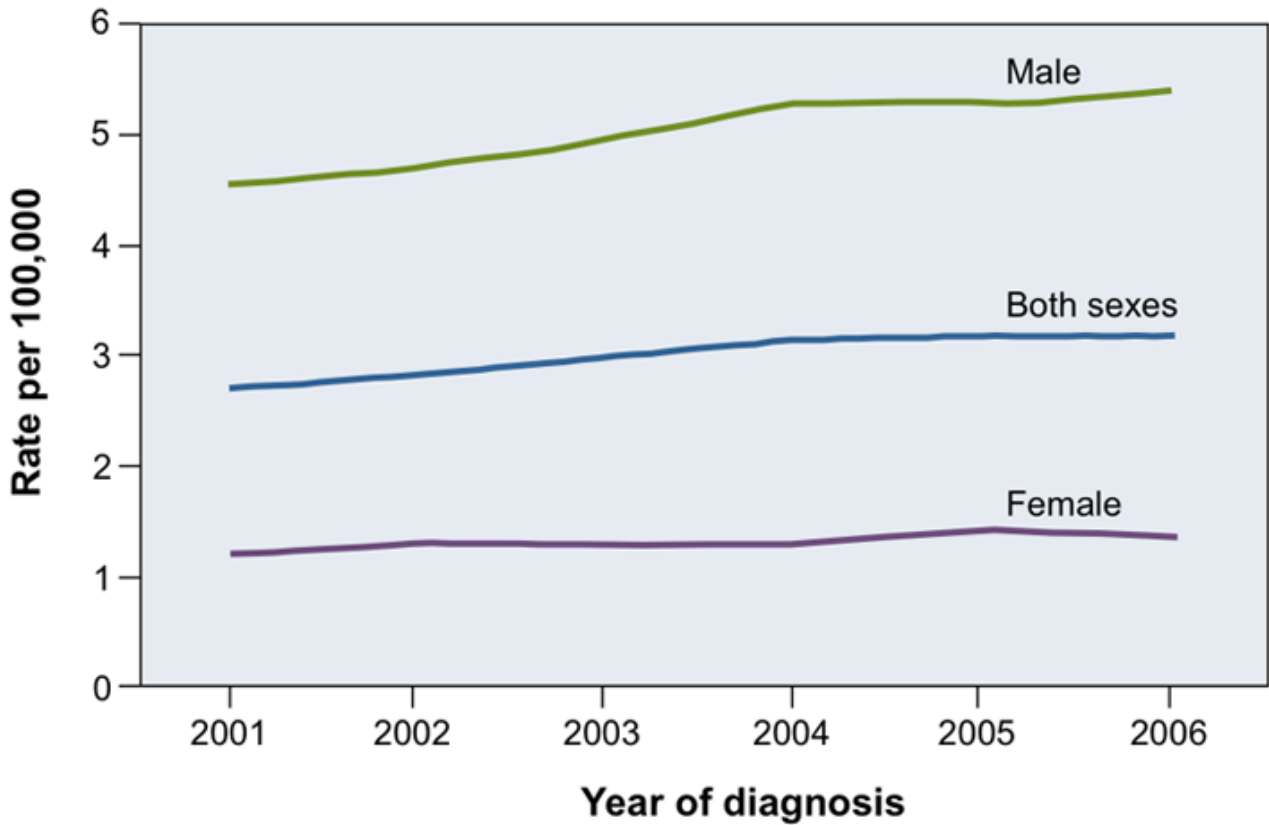


Figure 5 Impact of Screening on Stage of HCC at Time of Diagnosis

In a trial performed in Shanghai, China, more than 18,000 persons with chronic viral hepatitis (most of who 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.

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.

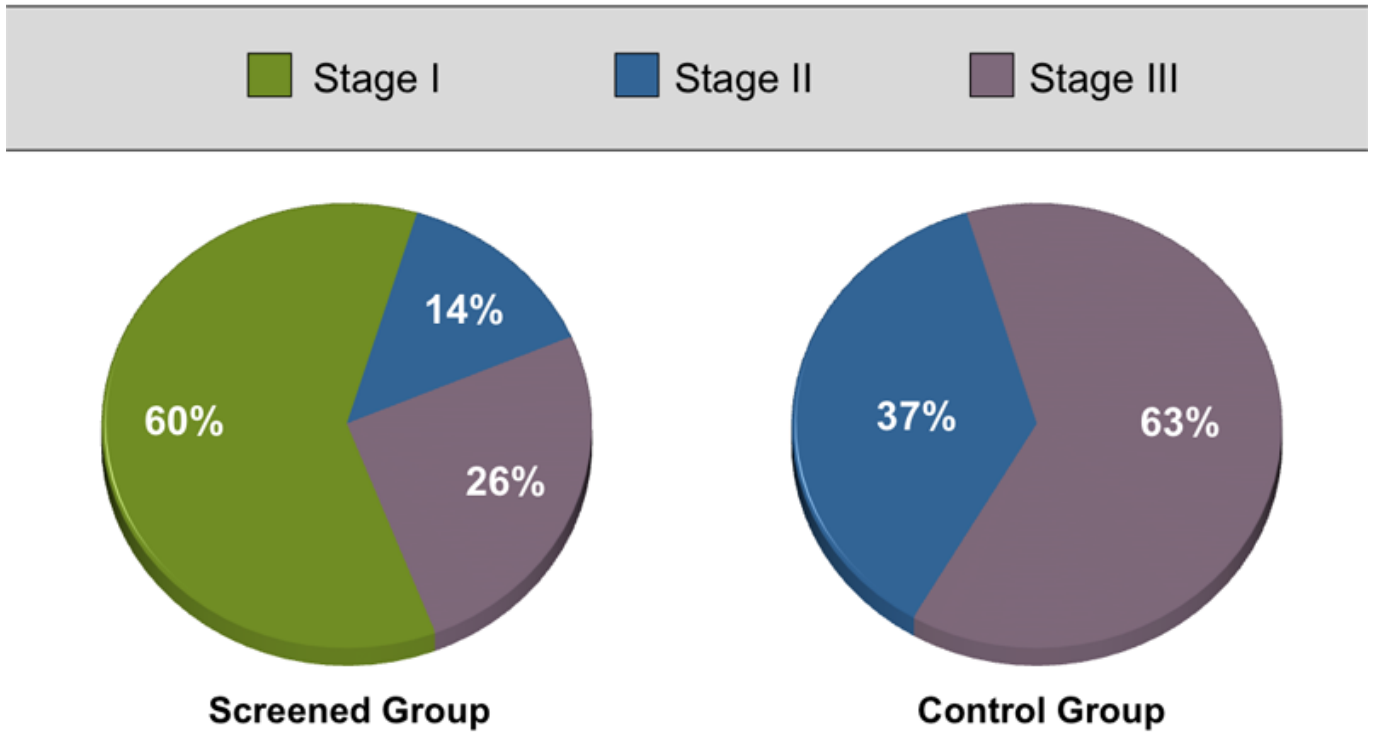


Figure 6 Impact of Screening on Survival after Diagnosis of HCC

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.

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol.* 2004;130:417-22.

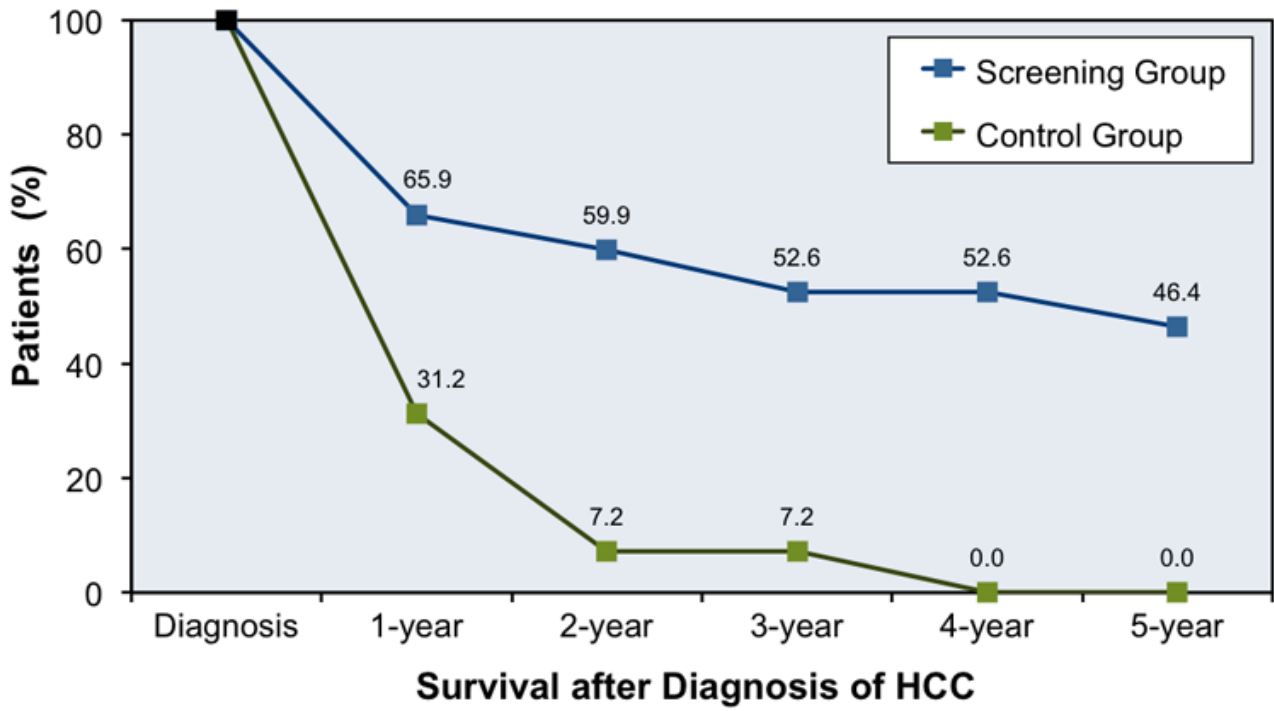


Figure 7 AASLD Diagnostic Algorithm for Suspected HCC Identified on Ultrasound

Abbreviations: CT = computed tomography; MDCT = multidetector CT; MRI = magnetic resonance imaging; US = ultrasound

Source: Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020-2.

