Chapter 2
Surveillance for Hepatocellular Carcinoma

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Background

Screening for cancer has become an integral part of medicine. Screening is a public health service in which members of a defined population are offered a test to identify individuals who are likely to benefit from further testing or treatment aimed at reducing the risk of a disease or its complications. Surveillance, on the other hand, is the continuous monitoring of disease occurrence using the screening test within an at-risk population to achieve the same goals as screening [1].

The ultimate goal of a cancer screening program is to reduce site-specific mortality. The benefits of screening should outweigh the costs before the use of a given test is promoted [1]. Ideally, screening will help to reduce morbidity and mortality by detecting asymptomatic disease or disease precursors and thereby allowing early treatment initiation in the natural history of a disease. Numerous screening tests have been investigated throughout the years, and many are now part of standard practice. These tests include the Papanicolaou test for cervical cancer, mammography for breast cancer, and colonoscopy for colorectal cancer. These methods have been shown to detect asymptomatic, treatable, early-stage disease and affect mortality [1]. On the other hand, if there is no effective treatment or if the disease is too rapidly progressive, then there is no value in screening [1]. If patients benefit from treatment before the onset of symptoms, then survival improvements should be associated with the gain in lead time compared to those diagnosed after the onset of symptoms. If there is no survival advantage and if life expectancy is not extended beyond when death would occur without early detection, then there is only the appearance of greater survival. This is referred to as lead time bias and serves as a major pitfall in many studies of screening and surveillance methods. In addition,

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Table 2.1 Recommendations for HCC surveillance in high-risk patients [2–5]

American Association for the Study of Liver Diseases (AASLD)	European Association for the Study of the Liver (EASL)	Asian Pacific Association for the Study of the Liver (APASL)	National Comprehensive Cancer Network (NCCN)
Ultrasound every 6 months	Ultrasound and AFP every 6 months	Ultrasound and AFP every 6 months	Ultrasound and AFP every 6 months

there are potential harms associated with screening such with perforation from a colonoscopy or unnecessary concern and anxiety over a lesion that may be detected on mammography. In addition, the specificity and sensitivity of all currently available screening tests are less than 100%, producing false-positive result and false-negative results, respectively. Therefore, it is important to screen populations which are considered at risk for the disease in question.

The World Health Organization has set criteria for a cancer screening program. First, the disease for which screening is being recommended should be an important health problem. Second, there should be an identifiable target population who is at risk for disease. Third, treatment of the occult disease should offer advantages compared with treatment of symptomatic disease. Fourth, the screening test should be affordable and must achieve an acceptable level of accuracy. Finally, the test must be acceptable to the target population and to health-care professionals, and standardized recall procedures should be used for when an abnormality is identified [1].

The utility of screening for hepatocellular cancer has been debated for many years and further fueled by the paucity of randomized controlled trials that show a clear benefit. However, despite this, HCC surveillance is widely applied to at-risk individuals and is currently recommended by most professional societies (Table 2.1).

Importance of HCC as a Health Problem

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor worldwide and accounts for 5.6% of all cancers [6]. The incidence of HCC has been rising since the early 1980s, and it is now the third leading cause of cancer-related mortality. In the USA, an estimated 18, 910 liver cancer deaths are expected in 2010 according to the American Cancer Society [7]. There is geographic variation in the incidence of liver cancer around the world and is highest in Mongolia with an age adjusted rate of 116.6 cases per 100,000 person–years for men and 74.8 cases per 100,000 person–years for women [8]. Eighty percent of cases are found in developing countries, with highest rates in Asia and sub-Saharan Africa [9]. These rates mirror the rates of chronic viral hepatitis [10]. Over the past two decades, the incidence of HCC has increased in the USA and continues to rise particularly in white middle-aged men most likely due to chronic HCV infection [11, 12].

At-Risk Population

In all areas of the world, the incidence is higher in males than females, with ratios varying from 1.4 to 3.3. The most common risk for development of HCC is cirrhosis, with annual risk for between 1% and 8%. In fact, more than 80% of HCCs arise in patients with cirrhosis of the liver [13]. In addition, the risk of developing HCC also varies according to the cause of chronic liver disease. Based on a theoretical cohort study, the current AASLD guidelines suggest that screening should be employed in cirrhotics when risk of HCC exceeds 1.5% per year [14, 15].

Chronic HBV

Chronic hepatitis B infection accounts for 52.3% of all HCC worldwide, and approximately 40% of patients with chronic HBV that develop HCC are not cirrhotic. The incidence of HCC in chronic HBV as a whole ranges from 0.26% to 0.5% per year, and these individuals are 100 times more likely to develop HCC than those who are uninfected [16, 17]. In patients with chronic HBV and cirrhosis, the incidence may be as high as 2.8% per year [18]. Aside from the presence of cirrhosis, factors which affect risk of HCC in chronic HBV include family history of HCC, ethnic background, HBV DNA level, HBV genotype, and presence of HBV mutants. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) trials study a prospective cohort of patients in Taiwan with chronic HBV who were recruited to a community-based cancer screening program. In this population, incidence of HCC increased in a dose response-dependent relationship as HBV viral load at entry increased. Cumulative incidence of HCC in patients with HBV DNA > one million copies/mL was 14.9% at the end of the 13th year of follow-up [19, 20]. Additional data from this group also shows that patients with HBV genotype C and precore or basal core promoter mutations are at higher risk of developing HCC [21]. The age at which an individual acquires HBV and the rate of active viral replication affect the age at which an individual develops HCC.

In a study comparing HBV carriers from Haimen City, China, and Senegal, West Africa, HCC mortality appeared higher in Haimen City than in Senegal, 878 vs. 68 per 10^5 person–years. There was a dramatic difference in HBV DNA levels at varying ages. In the Senegalese group, 14.5% were HBV DNA positive in their 20s, and this declined with each decade of age to 3.3%, 2.9%, and 0% thereafter. In the Chinese group, there was a higher prevalence of HBV DNA-positive males (29.4%) in their 1920s, and there was no consistent reduction seen per decade. The authors concluded that the prolonged maintenance of productive virus infection in Chinese carriers compared with Senegalese carriers might explain the higher risk of HCC in Chinese carriers [22]. This provides some further evidence that prolonged exposure to high HBV viral loads can influence HCC risk. In addition, environmental factors

such as exposure to carcinogens, diet, and lifestyle factors such as alcohol consumption, cigarette smoking, genetic and ethnic differences, and mode of transmission of HBV can affect one's risk of HCC and can make it difficult to compare cancer risk among different ethnicities.

The incidence of HCC in hepatitis B carriers also differs according to race. Asian women and men without cirrhosis who are considered chronic carriers without active replication or necroinflammation still appear to have an increased risk of HCC [2]. This does not appear to be as true of patients of Caucasian descent and may be related to the duration of infection. In addition, African patients with HBV seem to be at higher risk of developing HCC at a younger age. Based on cost-effectiveness studies, guidelines recommend that Asian men with chronic HBV in the absence of cirrhosis should undergo surveillance for HCC starting at age 40 and women at age 50. Africans with chronic HBV may develop HCC at an even younger age, and most recommend institution of screening from age 20 [23]. Regardless of age, however, all HBV carriers with underlying cirrhosis should be screened for HCC.

Data from the REVEAL-HBV group provides further insight into the HCC risk for individuals of Asian descent who are considered to be inactive HBV carriers. One thousand nine hundred and thirty-two patients who were seronegative for HBV e antigen, had serum levels of HBV DNA < 10,000 copies/mL and did not have cirrhosis, HCC or elevated serum levels of ALT were classified as inactive carriers, and compared to 18, 137 patients were HBsAg negative and negative for HCV with similar clinical features. Cox regression models were used to determine the risk of liver-related death and HCC. The mean follow-up was 13.1 years, and the annual incidence rates of HCC and liver-related death were 0.06% and 0.04% for inactive HBV carriers. The rate was 0.02% for both liver-related death and HCC for controls. The hazard ratio for carriers of inactive HBV compared to controls was 4.6 for HCC and 2.1 for liver-related death. This supports the theory that even inactive Asian HBV carriers have a higher risk of HCC and liver-related death compared with individuals who are not infected with HBV [24].

Newer studies have attempted to develop scores or nomograms to better define the risk of HCC in patients with chronic HBV. As part of REVEAL-HBV, study cohorts were allocated for model derivation and validation. Previously confirmed independent risk predictors—sex, age, family history of HCC, alcohol consumption habit, serum ALT level, HBeAg serostatus, serum HBV DNA level, and HBV genotype—were used in three regression models. Risk scores were created based on the regression coefficient from these models and were then used to predict an individual risk of HCC over 5- and 10-year periods. Overall risk was then depicted by nomogram and validated. In each of the models, either HBeAg seropositivity or HBeAg seronegativity with high viral load (HBV DNA level ≥ 100,000 copies/mL) and genotype C infection had the highest risk scores. These data show that the easy-to-use nomograms based on noninvasive clinical characteristics can accurately predict the risk of HCC in patients with HBV and may help determine who should be screened [25]. Other risk scores have been developed based on retrospective data from smaller study populations but are not well validated. Yuen et al. also examined various risk factors including gender, HBV viral load, HBeAg/Ab status, as well as

core and precore mutations, age, and presence of cirrhosis to predict risk of HCC. The study found that age, HBV viral load, core mutations, cirrhosis, and male gender appeared to be independent risk factors for development of HCC. The risk score had a sensitivity of 84% and specificity of 76% in predicting the 5- and 10-year risks for development of HCC [26].

Chronic HCV

Liver disease from chronic HCV infection accounts for 20% of all HCC. In the USA, an epidemic of HCV infection began in the 1960s and peaked in the 1980s with the highest risk of infection occurring in the people 20–30 years old [27, 28]. While most HCC occurs in patients with HCV in the presence of cirrhosis, there are also documented cases of HCC development in HCV patients without cirrhosis. Data from HALT-C showed that this 5-year cumulative risk of developing HCC with bridging fibrosis was 4.1% [29]. The yearly incidence of HCC in compensated cirrhotics is between 2% and 8%. A study by Sun et al. [30] showed that patients with hepatitis C and cirrhosis who have achieved viral clearance on therapy should continue to undergo surveillance. A more recent study published by Singh et al. [31] showed that HCV patients with cirrhosis who had SVR with therapy had a relative risk for HCC of 0.35 vs. nonresponders. However, 5% of the patients who did achieve SVR still developed HCC in long-term follow-up. Therefore, although the risk is decreased in patients with SVR, the authors of the study still continue to recommend regular surveillance. However, patients who clear HCV prior to developing cirrhosis have a very low likelihood of developing HCC and may not warrant surveillance.

Patients with HIV and either HBV or HCV are also at increased risk for HCC. In a large retrospective study conducted at the Veterans Administration Hospital, coinfection of HIV and HCV increased the risk of HCC fivefold compared to monoinfected patients with HIV and increased the risk of cirrhosis by 10–20-fold [32]. Current guidelines recommend entering coinfected patients with HBV/HCV and HIV using similar criteria for monoinfected patients with HCV or HBV [2]. Other risk factors for HCC in patients with chronic HCV include alcohol consumption, older age at infection, and the presence of porphyria cutanea tarda [33, 34].

Alcoholic Liver Disease

Alcohol intake is clearly a well-recognized cause of chronic liver disease and cirrhosis. It has been suggested that alcohol might be involved in the pathogenesis of HCC through a direct genotoxic pathway in addition to an indirect mechanism via cirrhosis [35].

Donato et al. investigated the association of alcohol use and risk of HCC. The study included patients hospitalized in Brescia, Italy, between 1995 and 2000.

Four hundred and sixty-four patients with a first diagnosis of HCC were compared to a control group of 686 subjects who had no underlying liver disease. The authors found that there was a linear increase in HCC risk with increasing intake of alcohol at >60 g of alcohol use/day even without underlying HBV or HCV. In addition, the odds ratio of HCC was increased twofold for each hepatitis virus infection for subjects who drank >60 g/day [35]. While the cohort was mostly men, there was no gender-based difference for risk of HCC with greater than 60 g of alcohol use. In a separate single center study, heavy alcohol consumption contributed to 32% of all HCCs, and there was synergy between heavy alcohol use, viral hepatitis, and diabetes in terms of increasing HCC risk [36].

NAFLD

Obesity is a risk factor for chronic liver disease and liver fibrosis without any other underlying etiology [37]. In a retrospective cohort study conducted in Paris, survival and complications in overweight cirrhotics were compared to normal-weight patients with either HCV-related or cryptogenic cirrhosis. While severity of liver disease did not differ between the overweight and lean groups, survival was decreased among the overweight group. In addition, a similar proportion of patients developed HCC in the overweight and HCV groups highlighting the carcinogenic potential of obesity-related cirrhosis. In addition, cirrhosis was detected later in life in overweight patients and at a more decompensated state compared to patients with HCV indicating a need for recognizing obesity as a cofactor for advanced liver disease and death [38].

As obesity continues to rise in the USA and the Western world, the incidence of cancer will continue to rise [39]. In a single center prospective study conducted in University of Michigan, 105 patients presenting with HCC were studied. The most common etiology of liver disease was HCV (51%) followed by cryptogenic cirrhosis (29%). Half of the patients with cryptogenic cirrhosis had features associated with nonalcoholic fatty liver disease (NAFLD). Patients who underwent surveillance had smaller tumors and were more likely to be eligible for surgical treatment with better median survival. The patients who had cryptogenic cirrhosis were less likely to have undergone HCC surveillance and had larger tumors. NAFLD accounted for at least 13% of the HCC cases [40]. The authors of this study concluded that the incidence of HCC in the USA may continue to rise even if the HCV epidemic levels off because of the increasing prevalence of NAFLD. This also highlights the current impact of NAFLD in the USA in terms of HCC risk.

A prospective study conducted at the Veteran Affairs hospital examined the risk of diabetes and chronic nonalcoholic liver disease [41]. 173,643 patients with diabetes and 650,620 without diabetes who were hospitalized in VA facilities between 1985 and 1990 were followed through 2000. Patients with known concomitant liver disease were excluded. The Kaplan–Meier survival analysis showed a significantly higher cumulative incidence of HCC among patients with diabetes compared to

patients without diabetes (2.39 vs. 0.87 per 10,000 person–years, respectively, $p < 0.0001$). The conclusions from this study showed that diabetes more than doubled the risk of chronic liver disease and HCC. The risk was highest among patients with more than 10 years of follow-up. The study further supports the association between diabetes, chronic liver disease, and HCC.

Other Causes of Cirrhosis

Other known causes of HCC include cirrhosis from genetic hemochromatosis, primary biliary cirrhosis (PBC), alpha 1-antitrypsin deficiency, and autoimmune hepatitis. Patients with genetic hemochromatosis and cirrhosis have a relative risk of 20 for HCC [42, 43].

As mentioned above, HCC occurs in patients with PBC. The incidence of HCC in stage 4 PBC is estimated to be between 3% and 5% per year and the frequency between 0.7% and 16% [44–46]. In a study of patients seen at the Mayo Clinic with PBC and HCC, the presence of HCC was predicted in 18 of 19 patients based on a model [44]. Age > 70, male sex, history of blood transfusions, and evidence of portal hypertension were associated with HCC. This study provides evidence that patients with advanced stages of PBC determined by histology or combinations of the above high risk are a target population for HCC surveillance.

Treatment of Early Disease

The purpose of screening and surveillance is to detect a disease early in its course in order to offer a beneficial treatment and ultimately decrease mortality. Once symptoms develop, the disease is often advanced and not amenable to curative therapy via resection, transplantation, or percutaneous ablation [2, 47]. There are no large randomized controlled trials comparing the different modalities of potential curative treatment including resection, transplantation, or radiofrequency ablation for early-stage disease. Surgical resection of HCC is preferred in noncirrhotic patients. Only 5% of the Western population fits this category though up to 40% of Asians do [2]. The 5-year survival after resection is acceptable (>50%). A prospective study conducted between 1989 and 2001 examined the outcome of patients with early HCC treated with partial hepatotectomy who would have also been candidates for transplantation. The median tumor size was 3.5 cm, and the average number of lesions was 1 with a range of 1–3. Approximately 86% of the patients had Child class A cirrhosis. The 1-, 3-, and 5-year survival rates were 85%, 74%, and 69%, respectively, with a median survival of 71 months. The 5-year disease-free survival was 48% with a median of 52 months [48].

In an intention-to-treat analysis comparing orthotopic liver transplant to surgical resection, 164 cirrhotic patients from 1989 to 1997 were evaluated for surgery.

Seventy-seven patients with Child–Pugh class A who were resected and 87 patients with Child–Pugh class B/C were selected for transplantation. The 1-, 3-, and 5-year survival rates for resection were 85%, 62%, and 51% and 84%, 69%, and 69% for transplantation. The overall 5-year survival for resection was 74% for the best candidates who did not have clinically relevant portal hypertension. The results from this study show that surgical resection and OLT provide similar and acceptable survival rates in cirrhotic patients with early HCC [49]. The well-accepted "Milan criteria" highlight the effectiveness of treating early disease. In a prospective cohort study between 1991 and 1994, the efficacy of liver transplant was evaluated in patients who had unresectable HCC. A total of 48 patients underwent transplant; 94% had cirrhosis secondary to HBV, HCV, or both. The criteria used to determine eligibility for transplantation were one nodule less than 5 cm and no more than three tumor nodules each 3 cm in diameter or less (Milan criteria). A total of 36 patients were Child class A of which 28 received anticancer treatment; 15 patients with Child C cirrhosis did not receive any treatment prior to transplant. After transplantation, the patients were followed for a median of 26 months (range 9–54 months). The overall mortality rate was 17%. After 4 years, the actuarial survival rate was 75%, and rate of recurrence-free survival was 83%, comparable to OLT outcomes in patients without HCC. Survival was not affected by patient's age, sex, type of virus, or Child–Pugh stage. The overall and recurrence-free survival rates at 4 years in patients who met predetermined criteria (Milan criteria), which included 35 of the patients, were 85% and 92%, respectively. In patients whose tumors exceed these limits (13 patients), the overall and recurrence-free survival rates were 50% and 59%, respectively. This study shows that early tumor stage was the most important factor affecting overall mortality and recurrence-free survival in patients being considered for transplant and emphasizes the importance of early detection to achieve potential cure [50].

Acceptability of Surveillance

Surveillance programs must be acceptable to health-care providers and individuals at risk. In the USA, it has become standard of care to screen patients with cirrhosis for HCC. In a national survey of 554 members of the AASLD, the majority of responders indicated that they routinely screened patients with cirrhosis using ultrasound and alpha-fetoprotein while 25% also used computed tomography [51]. Additional surveys have shown that gastroenterologists have adequate knowledge of at-risk patients, screening methods and modalities [52]. In Europe and Japan, while screening has become the standard of care for patients at risk of HCC, actual adherence rates are not known [53]. While it appears based on survey data that most hepatologists and gastroenterologists are aware of screening guidelines and abide by them, recent population-based data suggests that actual surveillance rates are much lower. In a study of 1,873 patients with HCC and a prior diagnosis of cirrhosis, only 17% received regular surveillance in the 3 years prior to diagnosis.

Patients seen in an academic center were more likely to have had surveillance. These studies highlight the fact that surveillance strategies are generally accepted but adherence is suboptimal [54, 55].

Effectiveness of Surveillance

The utility of surveillance for HCC in at-risk patients has been debated for some time. Effectiveness and cost effectiveness have been evaluated in various retrospective and prospective studies and models. Unfortunately, there is a paucity of randomized controlled trials in this area, leaving the available data plagued with bias. In this day and age, it is unlikely that additional randomized controlled trials of surveillance vs. no surveillance will be conducted due to ethical concerns. Nevertheless, the body of literature supporting the effectiveness of surveillance is vast. The ultimate objective of HCC surveillance is to decrease mortality from the disease.

Many studies indicate that regular surveillance of patients at risk of HCC increases the chance of detecting potentially curable or treatable tumors attempting to improve patient prognosis [56–59]. This phenomenon is referred to as "stage migration" and does not always correlate with improvements in survival [60].

Screening and surveillance have been recommended for these high-risk subjects; however, there have not been any studies which have shown a reduction in mortality by means of a randomized controlled trial except in HBV carriers in China [57]. Most studies of effectiveness in HCC are nonrandomized and not well controlled. These studies have generally looked favorably on surveillance and its effect on mortality though they generally suffer from significant bias. A retrospective study of 91 patients with HCC in Hawaii showed that patients who were screened had increased median survival when compared to those who were symptomatic (1,399 vs. 234 d, $p = 0.009$) [61]. Another study of patients with chronic viral hepatitis and HCC showed that patients who underwent surveillance were more likely to have smaller and fewer HCC. The adjusted median 2-year survival was also increased in the surveillance group after control for lead and length time bias, assuming tumor doubling time < 90 days [62].

A retrospective study conducted in Japan from 2001 to 2007 evaluated 240 patients who were infected with chronic HCV. These patients were divided into three groups which included patients who received routine surveillance with repeated imaging, another group which received regular doctor visits for chronic liver disease, and the last group which did not undergo any screening or routine medical visits. The prevalence of solitary tumors was significantly higher in the surveillance group, 66%, vs. 24% in the group who received no surveillance or medical visits. The size of the nodules was less than 2 cm in 64% of patients vs. only 5% in the screening and nonscreening groups, respectively. A significantly higher proportion of patients who were diagnosed at stages I and II were candidates for curative procedures [63]. The authors of this study also found that patients who

were screened at intervals greater than 12 months presented at later stages of the disease. In addition, HCC-related serological markers including AFP (cutoff at 200 ng/mL) and DCP (cutoff 40 mAU/mL) were negative in 47% of the surveillance group when these patients were diagnosed with HCC. This study showed the poor performance of tumor markers including DCP in detecting early-stage HCC and supported the AASLD guidelines that AFP alone should not be used for HCC screening when ultrasound is not available.

Recently, a retrospective cohort study investigated HCV-infected patients who developed HCC to evaluate the association between HCC surveillance and survival in a large nationwide VA clinical practice setting [64]. This study evaluated the effectiveness of HCC surveillance. Effectiveness takes into account the benefits and harms of an intervention. The study included 1,480 patients who were HCV infected and developed HCC during 1998–2007. Either surveillance with AFP or US was recorded in approximately 78% of the patients within 2 years before they were diagnosed with HCC. Only 2% of patients underwent annual surveillance with both AFP and US during the 2 years prior to HCC diagnosis. 5.7% had an AFP or US every 6 months and 34% had annual surveillance with one modality. In the 2 years before HCC was diagnosed, 57.7% received surveillance with AFP only, 19.4% with both AFP and US, and 0.5% received US only. It appears that most patients received inconsistent surveillance and the use of AFP alone was the most frequent modality. The timing of surveillance was examined in groups of patients based on receiving tests in two consecutive periods, 0–6 months only, 7–24 months only, both periods, and no tests in the two periods. The longest survival was seen in those who received surveillance tests in both time periods, while the shortest survival was observed in patients who received no surveillance in either period. These differences in survival were most pronounced for the 1-year survival rates (50.3% vs. 31.9%), less for the 3 years, and there was no significant difference in survival rates at 5 years. There was a significant 29% reduction in mortality risk among those who received surveillance tests in both time periods and a 20% risk reduction in those who received surveillance in the 0–6-month period only compared with no tests in either period. There was no significant difference in mortality for surveillance recorded only during the 7–24-month period before HCC diagnosis.

A few studies have looked at the effect of Child–Pugh classification score and have shown that surveillance prolongs survival in Child–Pugh class A patients but not in the sicker class C at time of diagnosis [26, 59, 65]. Because most patients with Child C cirrhosis have a severely reduced life expectancy as a result of underlying liver disease, most studies on surveillance have excluded these patients. For Child class B patients, prognostic benefit was seen in an Asian series, while there was borderline advantage seen in Italian Liver Cancer group series. One study has specifically evaluated surveillance for HCC in intermediate/advanced cirrhosis or Child–Pugh classes B and C [66]. In this study, a total of 1,834 HCC patients were seen consecutively from January 1987 to December 2004 at ten medical institutions. A total of 608 patients were selected from the registry, 468 class B and 140 class C cases. The patients were divided into two groups: group 1 included 252 patients in whom HCC was detected using regular surveillance based on liver US

and AFP performed every 6 months. Group 2 included 356 cases in whom HCC was detected incidentally, outside any programmed surveillance or during examination for other diseases or because of symptom appearance. The cause of liver disease included HBV, HCV and alcohol, cryptogenic, hereditary hemochromatosis, and PBC. In Child–Pugh class B, the cancer stage and treatment options were better in group 1 than group 2, and the medial survival was 17.1 vs. 12 months, and the 1-, 3-, and 5-year survival rates were 60.4% vs. 49.2%, 26.1% vs. 16.1%, and 10.7% vs. 4.3% in the respective groups. In the Child–Pugh class C patients, cancer stage and treatment distribution were better in group 1 than group 2, but the median survival did not differ, 7.1 months vs. 6.0 months. The authors of this study concluded that in the Italian health-care system, surveillance for early HCC diagnosis increases survival of Child–Pugh class B cirrhotics but not in patients who are Child–Pugh class C.

Liver transplantation is a widely accepted curative treatment for patients with early-stage HCC. Stravitz et al. evaluated the quality of surveillance for HCC and its effect on access to liver transplantation [67]. A total of 269 patients with cirrhosis and HCC were retrospectively categorized into three groups according to the quality of surveillance: standard of care, substandard surveillance, and absence of surveillance in patients who were not recognized to be cirrhotic. Standard-of-care surveillance was defined as performance of liver US or other abdominal imaging (CT or MRI) at least once during the year before cancer diagnosis which included a total of 172 patients. Forty-eight patients were categorized into the substandard surveillance group which was defined as absence of abdominal imaging within the year before cancer diagnosis in a patient with recognized cirrhosis and also included patients who had tumors identified on initial screening examination. The 59 patients underwent abdominal imaging for symptoms or an unrelated indication but were not recognized to have cirrhosis before the time of cancer diagnosis. HCC was diagnosed at stages 1 and 2 in 70% of patients in the surveillance group, 37% of patients in the substandard surveillance group, and 18% of patients in the no surveillance group. Liver transplantation was performed in 32% of patients in surveillance group vs. 13% in substandard surveillance vs. 7% in no surveillance group. The 3-year survival from cancer diagnosis in the no surveillance group was significantly less than the surveillance group (12% vs. 39%). The quality of surveillance had a direct impact on HCC stage at diagnosis, access to liver transplant, and survival.

To date only one randomized controlled trial of surveillance vs. no surveillance has shown a survival benefit to screening with six monthly ultrasound and AFP in a high-risk group in urban Shanghai, China [57]. This randomized controlled trial was conducted on Chinese patients with hepatitis B infection. The study included approximately 18,000 people aged 35–59 years with hepatitis B virus infection or a history of chronic hepatitis. People were randomly divided into two groups, surveillance vs. no surveillance group. The surveillance group was invited to have an AFP (cutoff 20 μg/L) test and undergo ultrasound exam every 6 months. The results showed that in the surveillance group, there were 86 cases of HCC vs. 67 and resection was achieved in 46.5% vs. 7% in the control group; liver transplant was not a treatment option. In addition, there were twice as many stage III cancers in the control

Table 2.2 Stage distribution, treatment, and survival of patients with HCC in the screened and control groups

	Screening group (86)	Control group (67)
Stage[a]		
Stage I	52 (60.5%)	0 (0%)
Stage II	12 (13.9%)	25 (37.2%)
Stage III	22 (25.6%)	42 (62.7%)
Small HCC	39 (45.3%)	0 (0%)
Treatment		
Resection	40 (46.5%)	5 (7.5%)
TACE/PEI	28 (32.6%)	28 (41.8%)
Conservative treatment	18 (20.9%)	34 (50.7%)
Survival (%)[b]		
1-year	65.9	31.2
2-year	59.9	7.2
3-year	52.6	7.2
4-year	52.6	0
5-year	46.4	0

[a] $\chi^2 = 61.41$, $p < 0.01$
[b] Log-rank $\chi 2 = 35.50$, $p < 0.01$
Reproduced with permission from Zhang et al. [57]

Table 2.3 Outcome of screening

	Screening group	Control group
Person–years in study	38,444	41,077
HCC occurrence		
No. of cases	86	67
Total incidence (per 100,000)	223.7	163.1
Rate ratio (CI 95%)	1.37 (0.99, 1.89)	
Deaths from HCC		
No. of deaths	32	54
Total mortality (per 100,000)	83.2	131.5
Rate ratio (CI 95%)	0.63 (0.41, 0.98)	

Reproduced with permission from Zhang et al. [57]

group vs. the screening group, 25.6% vs. 62.9%, respectively. The 1-, 3-, and 5-year survival rates were 65.9%, 52.6%, and 46.4% (surveillance) vs. 31.2%, 7.2%, and 0 in the control. There was a 37% reduction in HCC-related mortality in the surveillance group vs. the no surveillance group (Tables 2.2 and 2.3, Fig. 2.1).

Unfortunately, the adherence to surveillance was less than 60%. In addition, the sensitivity of AFP was 69%, and ultrasound was useful for screening. It would be ideal for these tests to be validated in other geographical areas including the West, but it seems unlikely that the West will conduct such randomized clinical trials. In a 16-year population-based study, assessing screening of HBsAg carriers

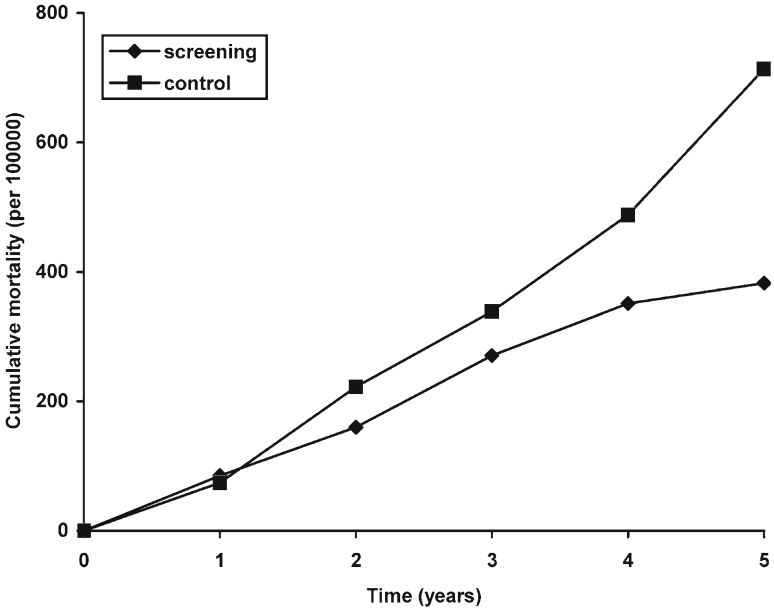

Fig. 2.1 Cumulative mortality in screening group and control group. Modified from Zhang et al. [57]

with semiannual AFP was effective in detecting tumors at a resectable stage and prolonged survival, although this study does suffer from lead-time bias [68]. With a large majority of HCC occurring in Asia in countries like China, many studies indicating effectiveness of screening and surveillance have been conducted in these locations. Another randomized controlled trial from China which included men with chronic HBV between ages 30 and 69 showed that surveillance with ultrasound and AFP resulted in early diagnosis but had no effect on mortality [69]. The screening group included 3,712 men who were screened in six monthly intervals with AFP. Ultrasound was recommended for an abnormal AFP. The population was followed for liver cancer or death. There were 3,712 subjects in the screening group with a mean follow-up of 61.9 months and 1,869 control subjects with a mean follow-up of 62.8 months. The AFP >20 μg/dL in 5.2% of subjects in group A and 5.7% in group B was not statistically significant. A total of 374 cases of liver cancer were diagnosed, with a higher incidence in the screened group vs. the controls although the results were not significant. In addition, the mortality rate among the groups was 1138.1 per 10 [5] in the screened group vs. 1113.9 per 10 [5] in the control group which was not statistically significant. The specificity and sensitivity of AFP in screening were 80.9% and 80.0%, respectively. The study, however, showed that a significantly higher number of cases in the screening group were diagnosed at stage I vs. the control group (27.9% in the screened group vs. 3.7% in the control group). Survival in patients with liver cancer from the screened group was better in the short term, but the advantage disappeared by 5 years. There was no

difference in overall mortality, and this is likely attributable to lack of effective treatment. This study, however, is limited because the screening regimen is considered suboptimal by today's guidelines.

Surveillance Tests

Various surveillance tests have been evaluated in the literature. Sensitivity and specificity are inherent to the test being performed. Sensitivity is the probability that a test is positive when true disease exists (true positive). Specificity, on the other hand, refers to the probability that the test is negative when the disease does not exist (true negative). Screening tests must be sensitive and reasonably specific. The accuracy of a test is related to the frequency of the disease in the population and is measured with positive predictive and negative predictive values. Currently, despite new recommendations from AASLD, both serologic and radiologic methods are used in surveillance of HCC. Unfortunately, most studies have evaluated these tests at the time of diagnosis rather than in an at-risk population being screened for disease.

Serologic Markers

The most widely used markers in HCC are alpha-fetoprotein and DCP. There are several reports on the sensitivity and specificity of AFP in surveillance. An AFP value greater than 200 μg/L can be highly specific for hepatocellular cancer, while levels less than 200 would not be informative enough to stop further investigation for HCC [70]. Serum AFP is no longer considered an appropriate surveillance test by AASLD because of the high rates of false-positive and false-negative results in patients with chronic liver disease. AFP level > 20 ng/mL performs poorly as a screening tool because of various reported sensitivities around 60%. Therefore, AFP used alone may miss up to 40% of HCC. Des-gamma-carboxy prothrombin (DCP) or prothrombin induced by vitamin K absence II (PIVKA II) has also been evaluated as a potential serological test. DCP is an abnormal prothrombin molecule generated by malignant cells. Most data regarding DCP comes from Asia, and experience in the West is limited. In a study done by Izuno and colleagues, the usefulness of DCP was evaluated in a group of 137 patients with liver cirrhosis. Patients were followed for an average of 3.4 years, and 35 of the patients developed HCC, with 16 developing a small tumor less than or equal to 2 cm in diameter. Eight patients had a significantly elevated DCP at the time of HCC detection, but these tumors were greater than 2 cm in diameter, and there were multiple or diffuse types. Tumors which were less than 2 cm in diameter were detected by imaging and elevated AFP. The authors concluded that DCP alone is not sensitive enough to detect early small liver cancers [71].

Another prospective surveillance study assessed the optimal test for detection of early HCC in 602 patients with chronic viral hepatitis during a 7-year period [72]. Patients had positive HCV antibodies or HBV surface antigen. Blood samples were obtained at 6- and 12-month intervals for serum AFP, and all patients had abdominal US at least once during each 12-month period. Out of the 602 patients, 426 patients were anti-HCV positive, 163 were hepatitis B surface antigen positive, and 13 were positive for both HCV and HBV. The follow-up range was between 12 and 103 months. A total of 31 cases of HCC were detected. AFP was elevated (range between 8 and 24 ng/mL) in 74% of HCC patients but was also elevated in 10% of non-HCC patients. The maximum sensitivity was 65%, and specificity was 90%. Abdominal US identified all 31 cases. The sensitivity and specificity of US were 100% and 98%, respectively. This study also supports that US was more accurate in detecting HCC, and AFP should not be used as the only test for screening and surveillance for HCC given its low positive predictive value (12%) and sensitivity.

Trevisani et al. studied serum AFP in patients with chronic liver disease. In a case–control study of 170 patients with HCC and 170 controls with chronic liver disease from HBV or HCV, the best discriminating AFP value was 16 ng/mL. A value of 20 ng/mL had a sensitivity of 62.4% and specificity of 89.4%. A 5% prevalence rate of HCC is seen in most liver clinics. In this study, the positive predictive value (PPV) was 84.6% with the 50% tumor prevalence of the study population but decreased to 25.1% at a 5% tumor prevalence. The negative predictive value (NPV) was 69.4% and rose to 97.7% at 5% tumor prevalence. In patients without viral hepatitis, the PPV was 100% at any HCC prevalence, while the NPV ranged from 59.0% to 73%. This study highlights that AFP misses many HCCs and may elevate in the absence of HCC, but elevations may be more indicative of HCC in patients without viral hepatitis [73].

The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial (HALT-C) study recently supported the efficacy of these serum markers as surveillance tests [74]. The study aim was to compare the accuracy of AFP and DCP in early diagnosis of HCC among patients with chronic HCV who were enrolled into the HALT-C trial. Among the 1,031 patients who were randomized in the study, 39 cases of HCC were detected, 24 of which were in early stage. These patients were compared to 77 controls. The sera were tested 12 months prior to HCC diagnosis. The sensitivity and specificity of DCP at time of diagnosis were 74% and 86% at a cutoff of 40 mAU/mL. On the other hand, the sensitivity and specificity of AFP at the time of diagnosis were 61% and 81% at a cutoff of 20 ng/mL. When the higher values of 150 mAU/mL for DCP and 200 ng/mL for AFP were used, sensitivity dropped to 43% and 22%, respectively. The sensitivity of DCP and AFP 12 months prior to diagnosis was lower still. While lowering cutoff values even further increased sensitivity to around 90%, the loss of specificity would likely lead additional testing in a large number of patients without cancer. While AFP and DCP alone were not very sensitive, the combination of the two was more so. If the markers were combined, the sensitivity increased to 91% at diagnosis and 73% prior to diagnosis with a decrease in specificity 74% and 71%, respectively. While neither marker showed impressive sensitivity, both markers increased significantly in patients with HCC,

Table 2.4 Sensitivity and specificity of DCP alone, AFP alone, and the combination of both markers in differentiating HCC cases from controls at two fixed cutoff values

Months from HCC diagnosis	Sensitivity	Specificity	Sensitivity	Specificity
DCP (mAU/mL)	>=40		>=150	
0	74%	86%	43%	100%
−3	65%	84%	39%	100%
−6	63%	88%	11%	100%
−9	52%	88%	6%	100%
−12	43%	94%	3%	100%
AFP (ng/mL)	>=20		>=200	
0	61%	81%	22%	100%
−3	58%	80%	13%	98%
−6	57%	76%	3%	100%
−9	45%	77%	6%	100%
−12	47%	75%	3%	100%
DCP and/or AFP	DCP>=40 *or* AFP>=20		DCP>=40 *and* AFP>=20	
0	91%	74%	43%	93%
−3	87%	69%	35%	95%
−6	86%	69%	34%	96%
−9	82%	67%	15%	97%
−12	73%	71%	17%	98%

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and tumor diagnosis was triggered by doubling of AFP in 5/39 (12.8%) of cases (Table 2.4).

Lens culinaris agglutinin-reactive AFP or AFP-L3 is an isoform of AFP which has also been studied as a tumor marker for HCC. AFP-L3 is reported as a percentage of AFP-L3 over total AFP level. Prior studies have shown that 10% is a cutoff for the presence of HCC [75]. AFP-L3 has not been well studied for use in surveillance. The clinical utility of AFP, DCP, and AFP-L3 in detecting HCC was assessed in patients with chronic viral disease, with and without HCC. Approximately 230 patients were divided into two groups: group 1 included HCC patients with chronic HCV or HBV, and group 2 included non-HCC patients with HBV or HCV who had chronic hepatitis or cirrhosis. HBV was confirmed with positive HBsAg and HCV with both positive HCV antibody and viral load. A total of 240 were tested for tumor markers. In patients who had HCC and HBV and HCV, the serum levels of DCP, AFP, and AFP-L3 were significantly higher. Using ROC analysis, the cutoff for AFP was 25 ng/mL yielding a sensitivity of 69%, specificity of 87%, and positive predictive value of 69.8% for detecting HCC. Patients with HBV or HCV with cirrhosis and no HCC also had higher AFP levels than in patients with chronic hepatitis. There was no correlation between size of single HCC and AFP, however, showing how it is not a good test for HCC surveillance. The cutoff for AFP-L3 was >10% and demonstrated a sensitivity of 56%, specificity of 90%, and positive predictive value of 56.1% in detecting HCC. However, AFP-L3 also did not correlate with size

of single HCC. Finally, for DCP at a cutoff of 84 mAU/mL, the sensitivity, specificity, and positive predictive value were 87%, 85%, and 86.8%, respectively. The DCP level remained below the cutoff value in all patients without HCC. In addition, DCP serum levels correlated with tumor size in single lesion HCC. DCP was not elevated in any patients without HCC [75].

The most recent iteration of the AASLD practice guidelines has recommended against the use of AFP as a surveillance tool in HCC. Despite this, most centers continue to use this tumor marker in combination with radiologic studies to survey for HCC. DCP is less commonly used in the West.

Radiologic Studies

Currently, ultrasound is the method of choice for screening because it appears to have adequate sensitivity, specificity, and accuracy. In addition, it is widely available and relatively inexpensive. Criticisms of ultrasound include that performance of the study can suffer from operator dependence as well as poorer quality images in patients with high body mass index, an increasing problem in the USA. There is a wide variation of sensitivity for ultrasound in published studies, ranging from 23% to 99%. Kim et al. published a study showing that the sensitivity and specificity for HCCs were 38% (6 of 16) and 92% (33 of 36), and those for dysplastic nodules were 0% and 95% (39 of 41), respectively, in a group of 52 patients with liver cirrhosis who were evaluated prior to transplant. Thus, they concluded that ultrasonography is insensitive for detection of HCCs and dysplastic nodules in patients with advanced liver cirrhosis [76].

Alternatively, other studies have shown that ultrasound can have a sensitivity of between 65% and 80% and specificity greater than 90%. A meta-analysis determined the performance characteristics of surveillance with ultrasound for the detection of early HCC defined by the Milan criteria [77]. Surveillance ultrasound detected the majority of tumors before they were clinically symptomatic with a pooled sensitivity of 94%. However, sensitivity was only 63% for detecting early HCC. In this study, AFP did not add additional benefit to ultrasound (Fig. 2.2).

Other imaging modalities are less well evaluated for HCC surveillance. In the USA, contrast enhanced CT or MRI is the modality of choice for diagnosing HCC. These tests are also used with varying frequency to screen for HCC, especially for patients active on the transplant list. According to the AASLD, the performance characteristics of computed tomography (CT) scanning in HCC surveillance are unknown, and thus, no recommendation can be made about CT scanning for individuals in whom US may not allow adequate visibility. In addition, CT exposes the patient to high doses of radiation at frequent intervals. MRI continues to be expensive when compared with ultrasound and is likely not cost effective for surveillance.

A study conducted by Chalasani et al. looked at 285 patients with cirrhosis who were evaluated for liver transplantation between 1994 and 1997. These patients were initially screened for HCC with AFP, US, and CT. One hundred and sixty-six

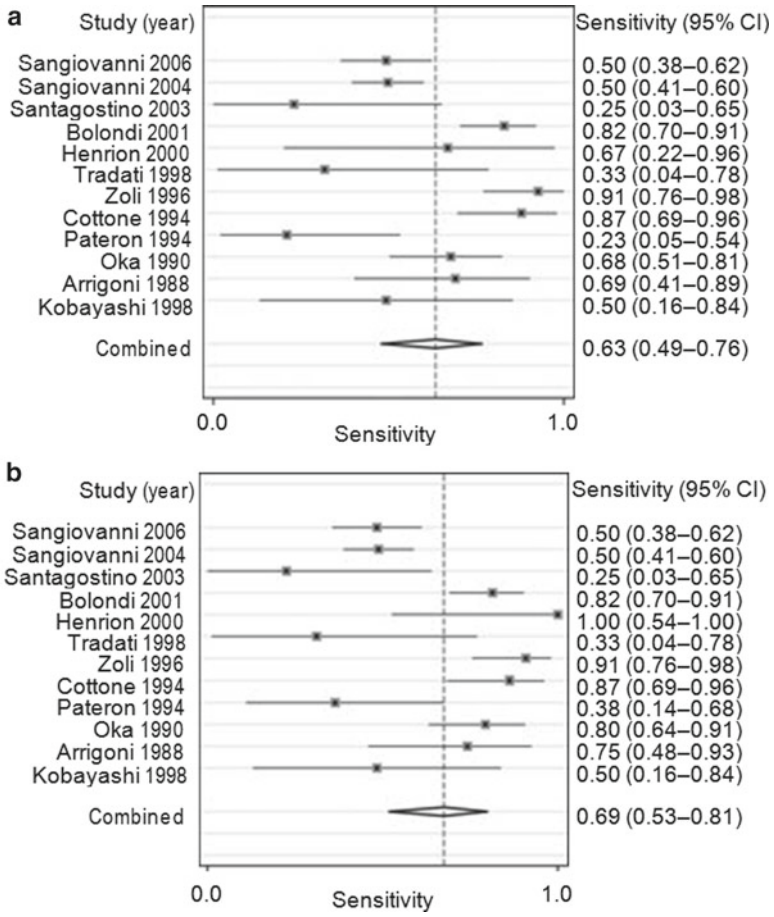

Fig. 2.2 Sensitivity of ultrasound with and without AFP for the detection of early-stage hepatocellular carcinoma (HCC):(**a**) forest plot for the sensitivity of ultrasound to detect early HCC; (**b**) forest plot for the sensitivity of ultrasound with AFP to detect early HCC. *Q*, chi-squared test of heterogeneity; I^2, inconsistency index. Reproduced with permission from Singal et al

patients who were eligible for liver transplant underwent continued screening with semiannual AFP and ultrasound during a median follow-up of 15 months. There were 27 HCCs found, 22 during initial screening and 5 during extended screening. The sensitivity of CT, AFP at a level of >20 ng/mL, and US were 88%, 62%, and 59%, respectively [78].

According to the AASLD, the performance characteristics of CT scanning in HCC surveillance are unknown, and thus, no recommendation can be made about CT scanning for individuals in whom US may not allow adequate visibility. Such patients tend to be obese with fatty liver disease and cirrhosis.

Timing

Surveillance guidelines by both the European Association for the Study of the Liver (EASL) and AASLD recommend the surveillance interval to be 6 months. This is based on data that the interval from undetectable lesions to those 2-cm diameter is approximately 4–12 months. However, experts in the Far East have adopted a 3-month interval for screening. There is no clear advantage in a 3-month program compared to semiannual surveillance [79]. In addition, a meta-regression analysis showed significantly higher sensitivity for early HCC with ultrasound every 6 months vs. annual surveillance [77].

A surveillance interval of 6–12 months has been proposed based on tumor doubling times in patients with HCV and HBV. In Italy, a study conducted in hemophiliacs with HCV showed similar efficacy between a 6-month and 12-month screening interval to identify potentially curable HCC [80]. Santagostino et al. based their study on prior data that all HCCs detected by yearly ultrasound surveillance of hemophiliacs with HCV and elevated alanine aminotransferase levels were multinodular. Therefore, they designed the study to evaluate if a more intense surveillance with AFP and US improved identification of single nodule tumors. Five hundred and fifty-nine HCV-infected hemophiliacs were divided into two arms: one followed at 6-month intervals and one at 1-year intervals. The overall incidence rate of HCC was 239 per 100,000 per year in the 6-month group and 143 per 100,000 per year in the 12-month group which was not statistically significant. The authors concluded that 6-month surveillance with US did not increase the chances of detection of single nodule tumors [79].

A study by Kim et al. evaluated whether semiannual surveillance affected outcome in patients diagnosed with HCC in Korea. In a total of 400 patients, more were diagnosed with HCC by surveillance with ultrasound and AFP (cutoff 20 ng/mL) every 6 or 12 months. They were divided into two groups: group 1 underwent surveillance every 6 months, while group 2 underwent surveillance annually. Single nodular HCC was more prevalent in group 1 (90.4%) vs. group 2 (72.9%), and curative treatment with resection of ablative therapy was more frequent in group 1 compared to group 2 (18.7% vs. 12.2%). Five-year survival was significantly better in group 1 vs. group 2, supporting that semiannual surveillance allowed for detection of earlier-stage HCC and survival compared to annual surveillance [81].

In a retrospective study comparing Child class A or B patients in Italy, semiannual surveillance was compared to annual surveillance with ultrasound with or without AFP. There were 510 patients in the semiannual surveillance group compared to 139 patients in the annual surveillance group. The cancer stage in the semiannual surveillance group was less severe with more single time <2 cm and less advanced tumors $p<0.001$. The median observed survival was 45 months vs. 30 months in the semiannual surveillance group compared to the annual surveillance group which shows a significantly increased rate of detection of early HCC decreased advanced tumors in the semiannual group. When the observed survival in the semiannual surveillance group was corrected for lead time bias, the survival

advantage remained (40.3 vs. 30 months, $p = 0.028$). These data support the currently recommended semiannual surveillance for high-risk patients to detect early-stage HCC [79].

Cost Effectiveness

Affordability of available testing is a common concern and is especially important if test use will be common as is the case with surveillance. There have been numerous studies assessing the cost effectiveness of surveillance of HCC in patients with cirrhosis. Many factors contribute to treatment outcome like compliance, heterogeneity and etiology of liver disease, and treatment effectiveness.

Patient compliance is a factor that also affects the effectiveness and cost effectiveness of surveillance. In a review by Thompson Coon et al. 1–15% of patients failed to comply with clinic-based surveillance programs in Europe and Japan compared to 42% of the population enrolled in a study in Shanghai [82].

Effectiveness of HCC surveillance is also influenced by the underlying etiology of the liver disease and the annual risk of HCC. There are many published decision analysis/cost-effectiveness models for HCC surveillance which differ in the theoretical population being analyzed and the intervention that is applied. The common theme among these studies is that the efficiency of surveillance is dependent on the incidence of HCC. Unfortunately, there are no experimental data to indicate what level of risk or what incidence of HCC should trigger surveillance. An intervention is considered effective if it provides an increase in longevity of 100 days [83]. In a modeling study of patients with Child class A cirrhosis, researchers found that with an HCC incidence of 1.5% per year, surveillance resulted in an increase in longevity of 3 months. If the incidence was 6%, the survival increase was 9 months [84]. A compilation of other studies has also suggested that in patients with cirrhosis of varying causes, surveillance may be effective when the risk of HCC exceeds 1.5% per year. For this reason, patients with cirrhosis should be offered cirrhosis when the risk of HCC is ≥1.5% per year. The incidence of HCC per 100 person–years in cirrhotic patients with HBV is up to 4.3% vs. 5–8% in HCV patients. In alcohol-related cirrhosis and PBC, the annual risk is up to 1.8% [34]. Patients who suffer from these diseases meet this incidence threshold and should undergo surveillance. However, this cutoff of 1.5% per year cannot be applied to HBV carriers without cirrhosis. In these patients, surveillance should be started once the incidence of HCC exceeds 0.2% per year according to AASLD guidelines [2].

Surveillance programs in which cost–utility ratios are measured at < $50,000 per quality-adjusted life year saved are thought to be cost effective [85]. In a Markov model study of patients with chronic HCV cirrhosis, screening with AFP and either ultrasound or CT was associated with incremental cost–utility ratios of 26,689 and 25,232 US dollars per quality-adjusted life year, respectively. Use of MRI increased

this number to $118,000 [15]. Another study found that biannual AFP with annual US provided the most quality-adjusted life year increase while maintaining the cost-effective ratio below the $50,000/QALY threshold. Increasing the frequency of ultrasound to biannual resulted in an increase in cost to $73,789 per QALY [14]. Another recent study from England was conducted in cirrhotic patients using a decision analytic model [86]. Comparisons were made between various surveillance algorithms using AFP with or without ultrasound at semiannual and annual intervals. The model estimated that compared with no surveillance, 6-month AFP and US tripled the number of people with operable tumors at diagnosis and halved the number of people who would die from HCC. At a willingness to pay threshold of 30,000 pounds per quality-adjusted life year (QALY), the most intensive surveillance protocol simulated with 6 monthly AFP and US was most cost effective in individuals with HBV-related cirrhosis.

Other studies have suggested that surveillance for HCC in patients with cirrhosis is not cost effective. In a study conducted by Bolondi et al., the cost effectiveness of surveillance in patients with cirrhosis was evaluated during 1989–1991 in Italy. The control group included 104 patients who had incidentally detected HCC vs. 313 patients with liver cirrhosis. Surveillance was conducted in 6-month intervals with US and AFP. Sixty-one cases of HCC were detected with an incidence of 4.1% per year of follow-up. Only 42 out of 61 patients were able to undergo curative treatment with surgical resection, liver transplantation, or local therapy. The survival rate of the 61 patients with the liver tumors was significantly longer than the controls. The overall cost of the surveillance program was $753,226, the cost per treatable HCC was $17,934, and the cost per year of life saved was $112,993 [58]. As these data show, the cost effectiveness of surveillance for HCC remains controversial, and the decision to proceed must weigh available resources and treatments.

Recall Policies

According to the WHO criteria for a surveillance or screening program, there must be policies set up to address abnormalities seen or identified on a screening test. This policy is termed a recall policy. Recall policies are the policies instituted to deal with an abnormal screening test result. The tests and interval follow-up are different. Recall policies cover investigations and follow-up that determine whether an initial abnormality identified on surveillance is an HCC or not. The process starts with an abnormal result, i.e., any nodule not seen on a prior study should be considered abnormal. Often, abnormalities such as a lesion seen on US are followed up by a CT scan or MRI, and if the results are still equivocal, biopsy is pursued. The AASLD has presented well-accepted guidelines for recall after an abnormal screening ultrasound (Fig. 2.3).

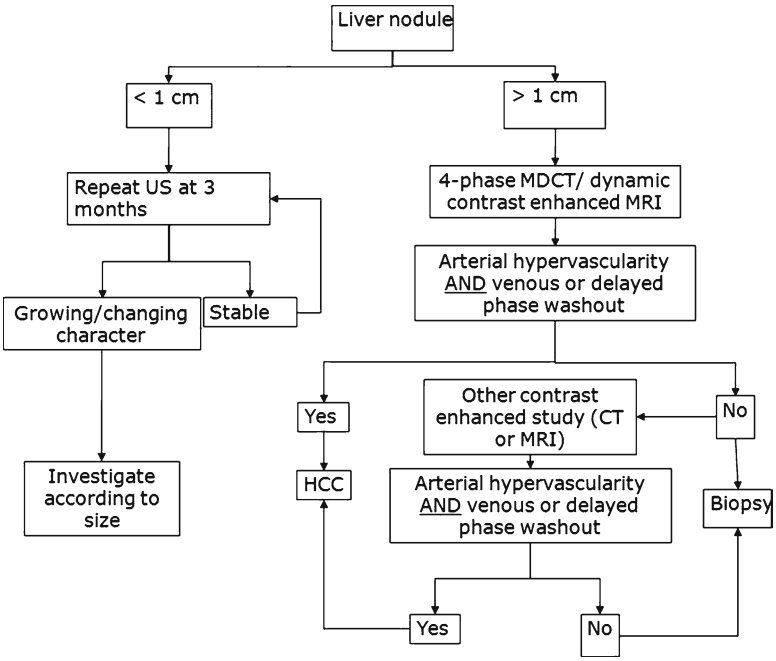

Fig. 2.3 Diagnostic algorithm for suspected HCC. Reproduced with permission from Bruix et al. [2]

Conclusion

HCC is one of the fastest growing cancers worldwide and is associated with a high mortality rate when detected after the appearance of symptoms. Much like other malignancies such as breast cancer, cervical cancer, and even colon cancer, early detection can allow for therapeutic benefit and appears to be cost effective in high-risk populations. High-risk populations for HCC differ geographically, as the etiology of HCC is different in developing vs. developed countries. HBV still accounts for the majority of HCC cases in Asia and the Eastern world, while HCV and NAFLD are currently on the rise in the Western world and account for a large proportion of cases of HCC. Therefore, surveillance for HCC is currently recommended by EASL and AASLD using ultrasound for identifying early stages of HCC, and this has become current standard of care in cirrhotics. Detecting HCC early allows for curative treatments such as resection, liver transplant, and RFA and may be associated with better survival. Thus far, however, only one randomized controlled trial has shown a mortality benefit in screening for HCC in HBV patients [57]. However, the remainder of the studies which are often retrospective reviews or cohort studies has shown a benefit in early diagnosis of HCC. Current guidelines recommend at-risk patients be screened by US at 6–12-month intervals, ideally

6-month intervals. The sensitivity of US is variable ranging from 65% to 80%, and specificity has shown to be greater than 90% [58]. AFP is no longer included in the surveillance guidelines given its poor sensitivity and specificity, as indicated by various studies. Other modalities such as CT and MRI have not been well investigated for screening for HCC, but are in place to further evaluate abnormalities detected on US. It appears that the majority of gastroenterologists and hepatologists provide some sort of HCC screening for their patients [78], though there have been several studies that have shown that surveillance is underutilized in the USA [55, 87]. About 28% of patients diagnosed with HCC underwent regular surveillance, and the patients who underwent surveillance were ten times more likely to be offered curative therapy [87].

Regular surveillance should play a role in reducing mortality from HCC, and it should be widely instituted [88].

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