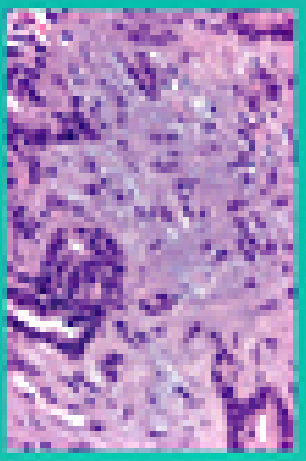
Contemporary Issues in Cancer Imaging

Primary Carcinomas of the Liver



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Primary Carcinomas of the Liver

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Primary Carcinomas of the Liver

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Series foreword

Imaging has become pivotal in all aspects of the management of patients with cancer. At the same time, it is acknowledged that optimal patient care is best achieved by a multidisciplinary team approach. The explosion of technological developments in imaging over the past years has meant that all members of the multidisciplinary team should understand the potential applications, limitations, and advantages of all the evolving and exciting imaging techniques. Equally, to understand the significance of the imaging findings and to contribute actively to management decisions and to the development of new clinical applications for imaging, it is critical that the radiologist should have sufficient background knowledge of different tumors. Thus the radiologist should understand the pathology, the clinical background, the therapeutic options, and the prognostic indicators of malignancy.

Contemporary Issues in Cancer Imaging – A Multidisciplinary Approach aims to meet the growing requirement for radiologists to have detailed knowledge of the individual tumors about which they are involved in making management decisions. A series of single subject issues, each of which is dedicated to a single tumor site, edited by recognized expert guest editors, include contributions from basic scientists, pathologists, surgeons, oncologists, radiologists, and others.

Although the series is written predominantly for the radiologist, it is hoped that individual issues will contain sufficient varied information so as to be of interest to all medical disciplines and to other health professionals managing patients with cancer. As with imaging, advances have been made in all these disciplines related to cancer management, and it is our fervent hope that this series, bringing together expertise from such a range of related specialties, will not only promote the understanding and rational application of modern imaging but will also help to achieve the ultimate goal of improving outcomes of patients with cancer.

Rodney H. Reznek
London

Preface to Primary Carcinomas of the Liver

The incidence of liver cancer in the United States and worldwide is increasing. The majority of primary liver cancers in the United States are hepatocellular carcinomas (HCC), with cholangiocarcinomas being the next most common. This trend is due to an increase in chronic hepatitis C, which along with hepatitis B is a major risk factor for liver cancer. Other contributing factors include heavy alcohol consumption, fatty liver disease, obesity, diabetes mellitus, and iron storage diseases. Although in general the mortality rates are high, survival rates in some countries are showing some improvement as more patients are being diagnosed with earlier stage tumors by means of aggressive surveillance with serologic tumor markers and diagnostic imaging. Advances in imaging techniques such as diffusion-weighted magnetic resonance imaging (MRI) and positron emission tomography–computed tomography (PET–CT) have helped in improving the detection and characterization of smaller earlier stage tumors. Treatment by means of resection or transplantation has excellent survival rates and, for patients who are not surgical candidates, ablative therapies and transarterial chemoembolization are suitable alternatives. Recently, for advanced HCC, anti-angiogenic agents have been employed with encouraging results. The role of radiotherapy in patients with cholangiocarcinoma and HCC who are poor surgical candidates is increasing.

The purpose of this edition of *Contemporary Issues in Cancer Imaging* is to review the epidemiology, screening, and diagnostic imaging techniques as well as roles of various therapeutic management strategies of common primary hepatic malignancies.

Hero K. Hussain
Isaac R. Francis

1

Epidemiology of hepatocellular carcinoma and cholangiocarcinoma

Jorge A. Marrero

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third cause of cancer-related deaths worldwide [1]. Cholangiocarcinoma (CCA) is the second most common primary liver tumor and is less common than HCC. The latest data from the Surveillance, Epidemiology and End Results (SEER) program, a population-based study on cancer incidence, prevalence, and mortality in the United States, show that primary liver cancer (90% HCC and 10% CCA) is one of few tumors with a rising incidence over the last 10 years (Figure 1.1). We herein discuss the epidemiology and risk factors for these tumors.

Hepatocellular carcinoma

The largest concentration of HCC cases in the world is in Asia, followed by Africa, Europe, and North and South America [2]. The incidence of HCC varies among ethnic groups, with increasing incidence rates found in Japanese (5.5/100 000 in men and 4.3/100 000 in women), African American (7.1/100 000 in men and 2.1/100 000 in women), Hispanic (9.8/100 000 in men and 3.5/100 000 in women), and Chinese (16.2/100 000 in men and 5/100 000 in women) populations. Even though the incidence rate is greater in men compared to women, there is a 2- to 5-fold higher incidence rate among women of various ethnicities compared to non-Hispanic white women. During the last two decades, an increasing trend in the incidence of HCC has been noted in Australia, Central Europe, the United Kingdom, Japan, and North America [3]. In addition, there has been an increase in HCC-related mortality in all countries during the same two decades. In the United States, the incidence of HCC has increased in recent years, and the distribution of patients with HCC has shifted toward younger patients, with the greatest increase in those between 45 and 60 years of age, likely due to the aging of the cohort infected with chronic hepatitis C (HCV) during the 1960s and 1970s [4]. The recent review of

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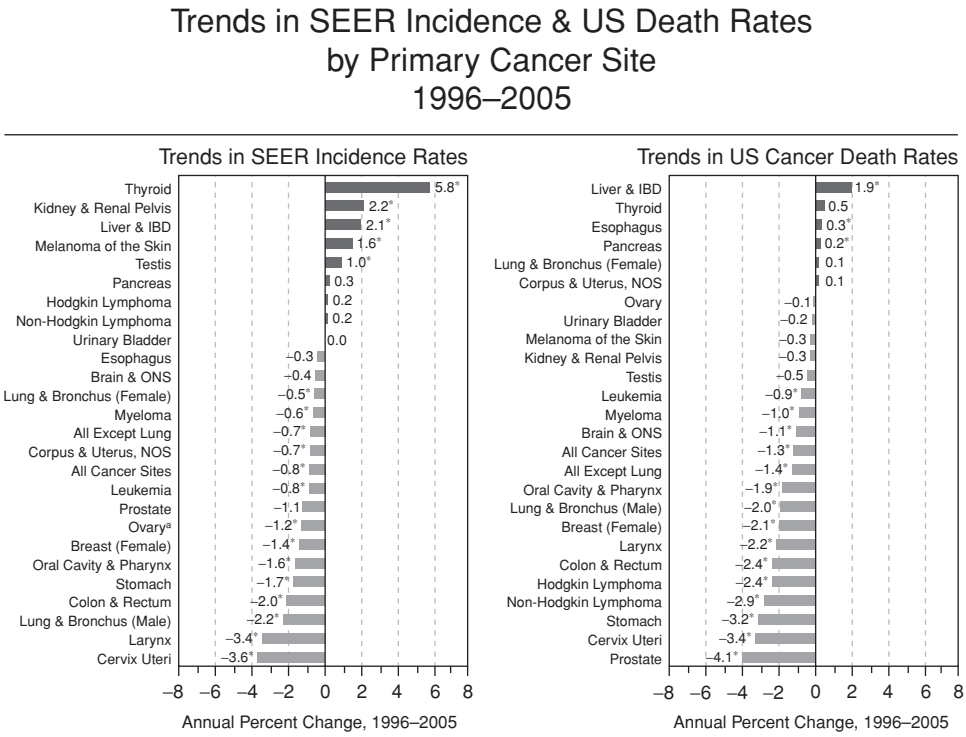

Figure 1.1 Trends in incidence and death rates from 1996 to 2005 based on the Surveillance, Epidemiology and End Results (SEER) program. Primary liver tumors (liver + IBD) account for the third highest increase in incidence and for the highest increase in death rates. Liver = hepatocellular carcinoma; IBD = intrahepatic bile duct cancer or cholangiocarcinoma; ONS = other nervous system; NOS = not otherwise specified.

the SEER program in the United States has shown that over the last 10 years HCC has been the tumor with the highest increase in incidence compared to other solid tumors.

Risk factors

The etiological agents leading to HCC have been largely established. In Japan, Europe, and America in approximately 60% of the patients with HCC, it is attributed to chronic HCV infection, in 20% it is attributed to chronic hepatitis B (HBV) infection, and in 20% it is attributed to cryptogenic and alcoholic liver disease. However, in Asia and Africa more than 80% of patients with HCC have underlying HBV infection [3,5]. The broad traits of the epidemiology of HCC can be traced to the prevalence of hepatotrophic viral infections. Chronic HBV infection is the

most common underlying etiology of HCC in the world [6]. In high prevalence areas such as Eastern Asia, China, and Africa, approximately 8% of the population is chronically infected as a result of vertical (mother-to-child) or horizontal (child-to-child) transmission. The pattern of transmission is different in areas with a lower prevalence of HBV such as North America, Western Europe, and Australia, where infection mostly occurs in adulthood through sexual and parenteral routes. The higher prevalence of chronic HBV, as well as the longer period of exposure to infection, largely explains the higher HBV-related HCC risk in endemic areas. Chronic HCV infection is found in a variable proportion of HCC cases in different populations, accounting for 75–90% of cases of HCC in Japan, 31–47% in the United States, 44–76% in Italy, and 60–75% in Spain [6]. HCC is the cancer with the highest increase in incidence rates over the last 10 years in the United States, and the driving force behind this increase is chronic HCV infection [7].

Cirrhosis is the most important risk factor for the development of HCC [8]. As shown in Table 1.1, the risk of HCC increases significantly in patients with cirrhosis. The risk of HCC in persons with HBV-related cirrhosis ranges from 2.2 to 4.3 per 100 person-years, whereas it is less than 1 per 100 person-years in non-cirrhotic patients. It is estimated that approximately 20% of patients with HBV-related HCC present without cirrhosis, indicating that other factors are important in hepatocarcinogenesis. The risk of HCC among patients with chronic HCV infection also occurs in the setting of cirrhosis as shown in Table 1.1. In Japanese studies, the summary incidence rate for HCC was 1.8 per 100 person-years in patients with chronic HCV infection and 7.1 per 100 person-years in persons with compensated cirrhosis. In the United States and Europe, the summary incidence rate was 3.7 per 100 person-years in patients with cirrhosis, which is lower than the rate in Japan.

The natural history of cirrhosis in patients with chronic HCV infection was assessed in 136 patients followed-up for a mean of 6.8 years [9]. The 5-year cumulative risk for HCC was 10%, the mean interval between the diagnosis of cirrhosis and development of HCC was 5 years (range, 0.5–10 years), and the median age for diagnosis of HCC was 63 (range, 50–74). Interestingly, more than half of the patients who developed HCC did not experience hepatic decompensation at the time of HCC diagnosis, indicating that HCC arising in cirrhosis can be clinically silent.

Alcoholic cirrhosis is another well-established major etiologic risk factor for the development of HCC [10]. Recently, an association between non-alcoholic liver disease and HCC has been made [11], but there are no cohort studies evaluating the natural history of non-alcoholic fatty liver disease. Other etiologies of chronic liver

Table 1.1 Incidence rates of HCC in prospective studies in patients with HBV and HCV infection

Setting	Geography	No. of studies	No. of patients	Mean follow-up (y)	HCC incidence[a]
HBV					
Carrier	United States	2	1804	16	0.1
	China	4	18 869	8	0.7
Chronic hepatitis	Europe	6	471	5.9	0.1
	Taiwan	2	461	4	1.0
	Japan	2	737	5.1	0.8
Cirrhosis	Europe	6	401	5.8	2.2
	Taiwan	3	278	4.3	3.2
	Japan	2	306	5.8	4.3
HCV					
Chronic hepatitis	Europe	1	239	4.2	0.1
	Japan	6	1451	6.2	0.8
	Taiwan	1	553	9.2	0.3
Cirrhosis	Europe/United States	13	1284	4.5	3.7
	Japan	7	626	5.8	7.1

[a] Incidence is per 100 person-years. Table modified from [8].

disease such as hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, and alpha-1 antitrypsin deficiency are less common causes of chronic liver disease with prevalence rates in patients with HCC ranging between 1 and 8% [12,13,14,15]. Improvements in the survival of patients with cirrhosis due to better specialty care may further increase the number of individuals at risk for developing HCC [16].

In addition to the presence of cirrhosis, host and viral factors are important in the process of hepatocarcinogenesis. Host factors including male gender and age greater than 50 years increase the risk for HCC [17]. In persons with chronic HBV infection, evidence of viral replication measured by the antigen status, high serum HBV DNA levels ($>10^5$ copies/mL) [18,19], and HBV genotypes (specifically B) increase the risk of HCC [20]. In contrast, viral factors in chronic HCV infection do not increase the risk of HCC. Other important risk factors in the development of HCC in patients with chronic viral hepatitis are the use of alcohol and tobacco.

Synergism between alcohol and viral hepatitis has been found to increase the risk of HCC [21]. Tobacco is another independent risk factor [22], as is obesity [23]. Aflatoxin B_1 (AFB_1) is a mycotoxin that grows on food stored in humid conditions and is a carcinogen predisposing to human HCC. AFB_1 ingestion has been associated with mutations in the coding regions of p53 tumor suppressor gene [24]. Diabetes has also been shown in prospective studies to increase the risk of HCC [25]. A recent study showed that there is synergy between alcohol exposure greater than 60 g of ethanol per day, greater than 20 pack-years of tobacco smoking, and obesity (body mass $> 30\,kg/m^2$) for increasing the risk of HCC in a predominant population of patients with HCV infection [26]. Therefore, multiple risk factors are important in the process of carcinogenesis in individuals with viral hepatitis.

The burden of HCV-related HCC in the United States is expected to continue to increase during the next decades. A recent study using molecular evolutionary analysis based on the coalescent theory ("molecular clock") investigated the time origin of HCV infection in Japan and the United States [27]. The authors showed an earlier onset of the HCV epidemic in Japan and, therefore, a longer duration of infection in affected individuals, which increases the likelihood for HCC development compared to that in the United States. The authors postulate that the incidence of HCC in the United States will also continue to increase over the next two to three decades. It has been estimated that the number of cases of HCC will continue to increase by 81% (from a baseline of ~13 000/year) by the year 2020, primarily due to the HCV epidemic [28]. This increase may lead to a significant health care burden in North America.

Cholangiocarcinoma

CCA is a neoplasm originating from the intra- or extrahepatic bile duct epithelium [29]. It was not until 1911 that primary liver neoplasms were distinguished based on their cellular origin into "hepatomas" and "cholangiomas" or "hepatocellular carcinomas" and CCA [30,31]. CCA may be considered a rare tumor comprising only 3% of gastrointestinal tumors; however, it is the second most common primary hepatic tumor accounting for 10–15% of primary hepatic malignancies, and its incidence is increasing. Its prevalence is geographically heterogeneous, with the highest rates in Asia, especially Southeast Asia [32]. In Western Europe and the United States, the incidence and mortality of CCA have increased over the last four decades.

In the United States, the age-adjusted incidence of intrahepatic CCA has increased by 165% from 0.32/100 000 (1975–1979) to 0.85/100 000 (1995–1999), with a dramatic increase between 1985 and 1993 [32,33]. An increasing incidence has also been observed in other regions around the globe. Estimated incidence rates in Crete and Greece have increased from 0.998/100 000 (1992–1994) to 3.327/100 000 (1998–2000) [34]. In Japan, the frequency of intrahepatic CCA diagnosed at autopsy increased from 0.31 to 0.58% between 1976–1977 and 1996–1997, respectively [35]. The incidence rates of intrahepatic CCA increased significantly in the United States between 1978 and 2000, with no significant change in the incidence of extrahepatic CCA. The cause of the global increase in the incidence rates for intrahepatic CCA is unclear, and the etiopathogenesis for most patients remains obscure.

Risk factors

The average age at presentation of CCA worldwide is 50 years. In Western nations, most cases of CCA are diagnosed at 65 years of age or older and only rarely before the age of 40 years [32]. In the general population, 52–54% of CCA are observed in male patients; however, mortality data show a higher estimated annual percentage change (EAPC) in women when compared with men with an EAPC of 6.9 ± 1.5 for men and 5.1 ± 1.0 for women [36]. Differences in the prevalence of CCA have been reported globally as well as between different racial and ethnic groups [37]. Globally, the highest prevalence has been described in Southeast Asia. Within the United States, a comparison of the 10-year prevalence between 1990 and 2000 showed a high age-adjusted prevalence of 1.22/100 000 for intrahepatic CCA in Hispanics [38]. Interestingly, within this group, the prevalence was higher in women. The lowest prevalence was described in African Americans, with a prevalence of 0.5/100 000 for men and 0.17/100 000 for women. Asian Pacific Islanders and Caucasians had prevalence rates ranging between these two groups.

In most patients, CCA develops without an identifiable etiology; however, certain risk factors have been established. The most commonly recognized risk factor is primary sclerosing cholangitis. The prevalence of CCA in patients with primary sclerosing cholangitis is 5–15% [39]. The annual incidence rate for CCA in the setting of primary sclerosing cholangitis is 0.6–1.5% [39,40]. Hepatobiliary flukes are another risk factor for CCAs. A strong association has been shown between the species *Opisthorchis viverrini* and *Clonorchis sinensis* and the development of CCA [41] especially in East Asia, which has the highest prevalence of these tumors and where flukes are endemic. These flukes are ingested with undercooked fish and

infest the bile ducts and occasionally the gallbladder [42]. Another risk factor for CCA that is also more common in Asian than Western countries is hepatolithiasis. An incidence rate of 10% has been reported in patients with hepatolithiasis [43,44,45]. Additional risk factors for CCA include Caroli's syndrome, congenital hepatic fibrosis, and choledochal cysts, all of which carry a 10–15% increased risk [46,47,48]. The association of intrahepatic CCA with chronic hepatitis C is controversial [49].

In summary, the incidence of both HCC and intrahepatic CCA is rising. The most important feature of HCC is that it occurs in the setting of a chronic liver disease, specifically cirrhosis, with viral hepatitis as the leading cause. Screening or surveillance of this group of patients may improve outcomes. In contrast, there are several risk factors for CCA, but the majority of cases occur without an identifiable risk factor. More studies are needed to identify persons at risk in order to develop screening or surveillance guidelines.

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2

Surveillance and screening for hepatocellular carcinoma

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The decision to screen an at-risk population for cancer is based on well-established criteria [1]. Although the overall goal is to reduce morbidity and mortality from cancer, the objective of screening is to use a relatively simple and inexpensive test in a large number of individuals to determine whether they are likely or unlikely to have the cancer for which they are being screened [2]. Screening is the one-time application of a test that allows detection of preclinical tumors, tumors at an early stage when they are asymptomatic with no clinical suspicion, and when curative intervention may achieve the goal of reducing morbidity and mortality. Surveillance is the continuous monitoring of disease occurrence (using the screening test) within a population to accomplish the same goals of screening [3]. Criteria have been developed, first promoted by the World Health Organization, to assess the benefits of screening for a specific disease [4]. This review will evaluate the process of screening/surveillance for hepatocellular carcinoma (HCC).

Cirrhosis has been recognized as the most important risk factor for the development of HCC [3]. Hepatitis C (HCV) and hepatitis B (HBV) are the major etiological agents that lead to the development of HCC [5]. HCV-associated cirrhosis is the causative agent that has been largely responsible for the increase in incidence of HCC in the United States. However, HBV is the leading cause of HCC worldwide, particularly in Asia and Africa. Therefore, there is a target population to which surveillance tests can be applied. Table 2.1 shows the recommendations for surveillance in patients with cirrhosis.

For surveillance to be effective, excellent treatment for early-stage tumors should be available. For early-stage tumors, surgical resection has provided 5-year survival rates of 70% in carefully selected patients with single small asymptomatic tumors (<5 cm in maximal diameter) preserved hepatic function and no evidence of portal hypertension [6]. Liver transplantation is the preferred method of treatment for patients not amenable to surgical resection but with tumors restricted to the

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Table 2.1 AASLD recommendations for the surveillance for HCC in patients with cirrhosis

Recommendation	Levels of evidence[a]
Surveillance for HCC should be performed using ultrasonography	II
AFP alone should not be used for screening unless ultrasound is not available	II
Patients should be screened at 6- to 12-month intervals	II
The surveillance interval does not need to be shortened for patients at higher risk of HCC	III

[a] Levels of evidence from I (highest) to III (lowest) [5]. AASLD, American Association for the Study of Liver Diseases.

Milan criteria (single nodule $\leq$5 cm or up to three nodules each $\leq$3 cm in diameter) [7]. The 5-year survival reported for liver transplantation is 74% [5]. Ablative treatments, specifically percutaneous ethanol injection and radiofrequency ablation, have 5-year survival rates of more than 37% in Barcelona Clinic Liver Cancer (BCLC) stage A patients not amenable to resection or transplantation [5]. Thus, therapies that result in excellent 5-year survival exist for patients with early-stage HCC, and an efficacious surveillance program is therefore critical for the identification of early-stage HCC.

The ideal surveillance test should be specific for preclinical HCC in the cirrhotic liver, regardless of the etiology of cirrhosis. It should be easily measurable, reproducible, minimally invasive, and acceptable to patients and physicians [8]. Both radiographic and serologic tests are currently used for HCC surveillance.

Ultrasound has been recommended as the primary radiologic screening test for HCC [5]. It is the least expensive, non-invasive, and widely available, which makes it an attractive screening test. To date, there has been no randomized controlled trial in patients with cirrhosis to assess the efficacy of ultrasound as a screening test, and its performance has been evaluated primarily in retrospective cohort studies as shown in Table 2.2 [9,10,11,12,13,14,15]. The reported sensitivities of ultrasound for the detection of early-stage HCC range from 29% to 100%, and the specificities range from 94% to 100%. The high degree of operator dependence and differences in equipment and body habitus are significant limitations that preclude it from being the optimal imaging surveillance test for HCC.

Table 2.2 Performance of ultrasonography as a surveillance test for HCC

Author	Cohort	No. early HCC cases	Sensitivity/ specificity (%/%)
Pateron *et al.* [9]	Childs A – B	14	29/96
Bolondi *et al.* [10]	Childs A – B	61	82/95
Tong *et al.* [11]	Child A	31	54/89
Cottone *et al.* [12]	Childs A	5	80/100
Kobayashi *et al.* [13]	Cirrhosis[a]	8	50/98
Sheu *et al.* [14]	Cirrhosis[a]	7	100/100
Oka *et al.* [15]	Cirrhosis[a]	40	68/NA

[a] The population of cirrhosis was not specified further. NA, not available.

Alpha-fetoprotein (AFP) has been the most widely used serologic test to screen for HCC. The operating characteristics of AFP are dependent on the cutoff level chosen to support the diagnosis of HCC. At higher cutoff levels, the test is more specific for HCC but at a cost of decreased sensitivity; at low cutoff levels, conversely, AFP becomes increasingly sensitive but with a higher rate of false positives [16]. A case–control study of 170 patients with HCC, of whom 60% had advanced HCC, and 170 matched patients without HCC demonstrated that the optimal cutoff was 20 ng/mL using receiver operating curve (ROC) analysis [17]. Therefore, a level greater than 20 ng/mL is the most commonly used cutoff in clinical practice to trigger a recall test for the diagnosis of HCC. A recent systematic review of five studies evaluating AFP greater than 20 ng/mL for the detection of HCC in patients with HCV-related cirrhosis showed sensitivities ranging from 41 to 65% and specificities ranging from 80 to 94% [18]. In addition, serum AFP values are frequently elevated among patients with chronic HCV with advanced hepatic fibrosis even in the absence of HCC, with the levels declining after antiviral therapy [19]. Better tests are needed to improve the detection of early-stage HCC.

The most reliable method to evaluate the efficacy of ultrasound and AFP for HCC surveillance would be a randomized controlled trial. There have been two large randomized controlled trials conducted in China using ultrasound and AFP among patients with chronic HBV [20,21]. In both trials, surveillance was conducted every 6 months and compared to patients who did not receive any routine screening. The first study evaluated 17 920 patients who were carriers of HBV; they were randomized to either surveillance ($n = 8109$) or no surveillance ($n = 9711$) and were followed up for an average of 14.4 months [20]. Of the patients randomized

to the surveillance group, 38 had had HCC; 76.8% of whom were at a subclinical stage, and 70.6% of those underwent resection. In the non-surveillance group, 18 patients had HCC, and none could undergo resection due to advanced disease ($p < 0.01$). Accordingly, the 1-year and 2-year survival rates for the surveillance group were 88.1% and 77.5%, respectively, compared to none more than 1 year for the non-surveillance group. The second randomized controlled trial evaluated 19 200 HBV carriers who were randomized to either surveillance ($n = 9757$) or no surveillance ($n = 9443$) [21]. A total of 86 patients developed HCC in the surveillance group, of which 45% were early stage, compared to 67 patients with HCC in the no surveillance group, of which none were early stage. The mortality rate of patients undergoing surveillance was significantly lower than that of patients in the control group [83.2 vs. 131.5 per 100 000, ($p < 0.01$), with a hazard ratio of 0.63 (95% confidence interval, .41–.98)]. These results demonstrate that the strategy of surveillance among patients with chronic HBV reduces overall mortality. The main problem with both studies is that they did not mention the number of patients who had cirrhosis or evidence of viral replication who are at the highest risk for developing HCC, and most likely both studies included patients who were asymptomatic carriers, who are at a lower risk for developing HCC. Therefore, the results are not generalizable to the majority of patients at risk for developing HCC.

Although randomized controlled trials have been performed in China on patients with chronic HBV, the results cannot be extrapolated to cirrhotic patients, who account for the majority of patients with HCC worldwide. No randomized trials have been performed in a cirrhotic population, so most of the data on surveillance in patients with cirrhosis come from cohort studies. The results of these studies are also fraught with lead-time and length-time biases that limit their generalizability with regard to improvement of survival with surveillance. The early-stage detection rate has ranged between 24 and 91% [22,23,24,25,26]. Therefore, the impact of surveillance on mortality in patients with cirrhosis has been assessed in only non-randomized trials to date.

Surveillance for any tumor should be cost effective. The standard threshold for cost-effectiveness has been determined to be a maximum of $50 000 per quality-adjusted life year (QALY). Economic models studying the benefits of surveillance programs in HCC have been developed. Surveillance with biannual AFP and ultrasonography in Child-Pugh Class A cirrhotics increases the mean life expectancy with cost-effectiveness ratios between $26 000 and $55 000 per QALY [27]. When a similar analysis was performed in HCV cirrhotics, the cost–utility ratio was $26 689 per QALY [28]. Therefore, screening with ultrasonography and AFP has been shown to be cost-effective in compensated cirrhotics. Other imaging modalities, such as