Surveillance for Hepatocellular Carcinoma

22

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Contents

22.1 Introduction

The global incidence and mortality rates of hepatocellular carcinoma (HCC) overlap worldwide, a fact that clearly indicates that majority of patients are identified with an advanced cancer that almost invariably prevents potentially curative treatments, thereby resulting in an average survival of 1 year from diagnosis [1–4]. The only hope for a cure, in fact, rests on early diagnosis as it may be obtained through surveillance of patients at risk, an end-point that unfortunately is achieved in a minority of patients, most clustering in the developed world [5]. Yet, population-based studies indicate that even in economically developed regions only a minority of patients with an HCC will ultimately undergo regular screening and curative treatments, despite most doctors and patients are fully aware of the benefits of screening for such a potentially lethal disease as HCC [6, 7]. This clearly underlines the existence of barriers to screening like limited or outdated knowledge, lack of financial incentives, limited access to appropriate testing and treatment, which altogether work against screening effectiveness. This is no surprise, since surveillance involves more than simply a screening test, whereas it is framed in a program where tests, recall policies, and quality control procedures are standardized, with significant economic consequences [8].

22.2 Target Population

HCC is unique in that it develops in the context of well-known and readily identifiable environmental risk factors. Indeed, majority of HCCs occur in patients with chronic liver disease including cirrhosis caused by chronic infection with the hepatitis B (HBV) and C (HCV) viruses and excess of alcohol intake [9, 10]. More recently, metabolic diseases related to insulin resistance, including diabetes and obesity, have been recognized to be causally related to HCC as well, in most patients bridging HCC to the histopathological diagnosis of non-alcoholic steatohepatitis

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Table 22.1 Groups for whom HCC surveillance is recommended or in whom the risk of HCC is increased, but surveillance benefit is incertain [8]

	Threshold incidence for efficacy of surveillance (>0.25 LYG) (%/year)	Incidence of HCC
Surveillance recommended		
Asian male hepatitis B carriers > 40 years	0.2	0.4–0.6 %/year
Asian female hepatitis B carriers > 50 years	0.2	0.3–0.6 %/year
Hep B carriers with family history of HCC	0.2	Higher incidence than without family history
African/North american blacks with hep B	0.2	HCC occurs at a younger age
Cirrhotic hep B carriers	0.2–1.5	3–8 %
Hep C cirrhosis	1.5	3–5 %
Stage 4 primary biliary cirrhosis	1.5	3–5 %
Genetic hemocromatosis and cirrhosis	1.5	Unknown, but probably > 1.5 %/year
Alpha 1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5 %/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hep B carriers younger than 40 (males) or 50 (females)	0.2	0.2 %/year
Hep C and stage fibrosis 3	1.5	<1.5 %/year
Non-cirrhotic NAFLD	1.5	<1.5 %/year

(NASH) [11–14]. Since the decision to enter a patient into a surveillance program is driven by the level of risk for HCC (Table 22.1), the incidence of HCC is generally taken as a starting point to select the target population to be screened. In the absence of experimental data to indicate what level of risk or what incidence of HCC should trigger surveillance [15], decision analysis/cost models have extensively been used to identify the incidence cut-off of HCC at which surveillance is worth [16]. While any intervention is considered effective whenever it provides an increase in longevity of about 100 days, the same intervention is considered cost-effective if achieved at a cost of less than US $50,000/year of life gained [16]. In Caucasian patients with Child–Pugh A cirrhosis, a 1.5 %/year incidence of HCC has been associated to about 3 month increase in longevity in a patient population lacking access to liver transplantation [17], whereas in a similar analysis including liver transplantation in a population of hepatitis C patients with cirrhosis, surveillance with either computed tomography (CT) scan alone or CT scan plus ultrasound (US) became cost-effective at HCC incidence rates of more than 1.4 %. Mitigating however the clinical impact of these models where the performance characteristics of CT scan being evaluated in diagnostic studies, not in the context of screening programs [18]. While biannual surveillance combining alpha-fetoprotein (AFP) with US was deemed cost-effective regardless of HCC incidence, by others [19]. Therefore, with all the caveats of data obtained through modeling, it seems reasonable to offer semiannual surveillance to patients with cirrhosis of varying etiology whenever the risk of HCC is 1.5 %/year or greater [8, 20].

Owing to the fact that cost-effectiveness analyses were restricted to cirrhotic populations, there are only sparse data on whether surveillance is worth in cirrhosis-free patients with chronic viral hepatitis. To our knowledge there is one cost-effectiveness analysis of surveillance for hepatitis B carriers using US and AFP levels only, which suggested cost-effectiveness of surveillance every 6–12 months in populations with an incidence of HCC exceeding 0.2 %/year (J. Collier and M. Sherman, unpublished observations). Currently, the American (AASLD) and the European (EASL) Associations for the Study of the Liver recommend surveillance for patients with cirrhosis of any etiology and for selected hepatitis B carriers using abdominal US at 6-month intervals, whereas the use of serum AFP as a surveillance test is discouraged [8, 20]. It should be acknowledged, however, that real-life studies of surveillance of patients with compensated cirrhosis of any etiology have highlighted high rates of non-HCC-related mortality that fuel the argument of cost-effectiveness of screening for liver cancer in the cirrhotic population [21]. Arguments are likely to be boosted by EASL recommendation of screening also hepatitis C patients with bridging fibrosis in addition to those with histological or clinical evidence of cirrhosis, since the transition from advanced fibrosis to cirrhosis could not be accurately documented in all patients [20]. The Asian Pacific Association for the Study of the Liver (APASL) endorses surveillance for cirrhotic patients with HBV and HCV maintaining the combination of US and AFP every 6 months [22]. Finally, surveillance for HCC is not endorsed at all by the National Cancer Institute which in fact questions the robustness and limited generalizability of data obtained so

far to elaborate the current guidelines, arguing on the lack of evidence that HCC mortality is decreased by surveillance [23]. This position is shared by others in the USA [24].

22.2.1 HBV Carriers as Target

The annual incidence of HCC in patients with chronic hepatitis B ranges from 2 to 5 %, in strict correlation with the histological stage of the underlying liver disease [25]. In Europe, HBV-related HCC is associated with cirrhosis in the majority of the patients [26, 27], whereas this is not true in Asia and Africa where the tumor is common also among carriers with mild hepatic fibrosis, likely as a consequence of long-standing infection that is often acquired perinatally [28–30]. Recently, it has been clearly demonstrated that also Asian carriers with inactive hepatitis, i.e., those with persistently normal ALT and serum HBV DNA < 2000 IU/ml develop HCC, yet at lower rates compared to patients with elevated viremia [26, 27, 31, 32]. In HBV patients, HCC risk may be modulated by additional risk factors like age, co-infection with hepatitis C or HIV, alcohol abuse, or co-presence of metabolic liver diseases. According to AASLD and EASL, surveillance is recommended independently on the level of fibrosis and ethnicity, to all adults with active hepatitis B. The REVEAL study and other population studies have clearly shown the existence of a direct relationship between the risk of developing HCC and viral load, even when this predictor was measured years before tumor diagnosis [32, 33]. This was clearly anticipated by prospective studies of cohorts of carriers from Europe and Asia in which the presence of serum HBeAg and high levels of HBV DNA were found to independently predict the subsequent development of cirrhosis and HCC [32, 34–37]. The fact that most carriers in Far East likely acquired HBV infection perinatally and had a mean age at enrollment of 40 years, drove the attention towards high levels of HBV replication persisting for more than 4 decades as a predictor of increased HCC risk [38, 39]. An intriguing finding of some studies, however, was the persistence of HCC risk in aged patients following HBsAg seroconversion, supporting both the carcinogenic role of occult infection with HBV and the need for continued surveillance of these patients [40, 41]. This is not the rule in Caucasian patients who were successfully treated with antivirals, in whom a decline of HCC risk following HBsAg seroconversion was annotated, likely reflecting differences in HBV epidemiology and modality of infection between Asian and Caucasian populations [42–45] (by courtesy of WR Kim, Stanford University). The fact that the yearly risk of HCC in male carriers in Southeast Asia starts to exceed 0.2 % at the age of 40 years, irrespectively of liver disease activity (J. Collier and M. Sherman, unpublished observations), led AASLD to endorse screening of Asian men from the age of 40 onwards. On the other hand, surveillance is recommended for 50 year-old Asian women due to their lower incidence of HCC compared to men. In patients with a family history of HCC, surveillance should be offered at a younger age, although the preferred age cut-off is not established [28, 46]. Since in African carriers HCC develops at a younger age compared to Caucasians, surveillance in these populations is deemed necessary at younger age than elsewhere. This is not the case for blacks born outside Africa [29, 30].

The HBV genotype has been implicated as a driver of cancer risk, probably as a consequence of genotype-related differences in duration and severity of HBV-related hepatic inflammation over time. Studies from Asia involved the genotype B in anticipated HBeAg seroconversion, higher rates of sustained remission after HBeAg seroconversion, less active hepatic necroinflammation, slower progression to cirrhosis, and lower rates of HCC development compared to genotype C of HBV [47–52]. Growing evidence suggests that genotype A infections have a generally more favorable outcome than genotype D infections in the West [53, 54]. With all the caveats due to a bias of patient selection, studies in Asia and West recognized that long-term administration of nucleo(s)tide analogs prevents the onset of HCC in patients with chronic hepatitis B, not in cirrhosis where the rates of cancer are lower than in untreated patients [55–57]. All liver societies, therefore, recommend continuing surveillance in treated patients including cirrhosis achieving HBsAg seroclearance.

22.2.2 HCV Carriers as Target

AASLD, EASL, and APASL, all endorse screening for patients with hepatitis C-associated cirrhosis. While the incidence of HCV-related tumors is declining in southern Europe and Japan, HCC is on the rise in other geographical areas including United States and northern Europe, all these changes being related to a modification of population exposure to viral hepatitis and alcohol [55]. Several retrospective and prospective studies indicate a wide range of HCC incidence in patients with hepatitis C-related cirrhosis which in fact spans from 2 to 8 % [58–60]. Conversely, there is a single prospective population-based study evaluating the risk of HCC in patients with chronic hepatitis C [61]. That study carried in 12.008 serum anti-HCV-positive men, demonstrated a 20-fold increased risk of HCC compared to anti-HCV negative subjects, without showing any correlation with presence or absence of cirrhosis. The HALT C study, originally designed to test the efficacy of chronic interferon dosing in patients with a previous failure to antiviral therapy, did confirm the occurrence of HCC in non-cirrhotic patients with chronic hepatitis C (5-year risk of 4.8 %), providing also the opportunity of constructing a risk score for HCC by combining factors like older age, African-American

ethnicity, lower platelet count, high alkaline phosphatase activity, and presence of esophageal varices [62].

Studies carried out in the West and Asia demonstrated that the risk of HCC is attenuated in cirrhotic patients with a response to interferon-based regimens [63]. However, since viral eradication does not completely eliminate the risk of HCC in older patients and those with advanced fibrosis, surveillance is worth to be continued in patients with cirrhosis following interferon related clearance of HCV-RNA [8, 20]. Liver cancer has been reported in fact to occur years after treatment completion, in some studies at a rate between 0.66 and 1.24 per 100 person years [46, 64], in others at rates between 0.6 and 2.5 % per year [65, 66]. In a French single center cohort study [55] and in many retrospective *studies* [64, 65] in cirrhosis, liver-related complications, including HCC occurred even after achievement of an SVR, reflecting the carcinogenic effect of the extensive architectural changes of the cirrhotic liver that may persist following an SVR. Another prospective Japanese study confirmed these results [67]. The similar cumulative incidence rates of HCC in patients with bridging fibrosis and those with cirrhosis highlight the need to treat HCV patients before the stage of bridging fibrosis. In one study [68] HCC after SVR was seen in patients with persistence of cirrhosis, not in those in whom cirrhosis reverted following antiviral therapy. In a retrospective study of more than 800 SVR patients in Japan occurrence of HCC was associated to a more severe liver disease score composed by age, platelet count, liver fibrosis, and AFP [69]. As the risk of HCC is high in HCV-cirrhotics who fail to achieve an SVR to interferon-based therapy [63, 64, 70–72], alternative treatment regimens have been explored. The administration of a long course of low dose of PegIFNα2a provided no benefit to the overall population, even though a small benefit in terms of HCC reduction was seen in patients classified as cirrhotics at baseline compared to those with advanced fibrosis (cumulative HCC incidence: 6.8 % vs. 15.5 %, $p = 0.01$) [73]. However, a similar study with PegIFNα2b failed to demonstrate any HCC prevention in both patients with cirrhosis and those with advanced liver fibrosis [74].

22.2.3 HIV and Viral Hepatitis as Target

In HIV infected patients liver-related morbidity and mortality significantly increased during the HAART era as a consequence of an important reduction in HIV-related complications, making co-infection with HBV (6–14 %) and HCV (25–30 %), to emerge as hepatotoxic factors in addition to excessive alcohol consumption, non-alcoholic fatty liver disease, and drug-induced liver injury [75].

While the MORTAVIC study in 2001 indicated HCC to be responsible for 25 % of all liver deaths, in the HAART era studies suggest that HCC developing in co-infected patients is more aggressive, presents at an earlier age and is less frequently curable than HCC in HCV mono-infected patients [76, 77]. If confirmed, these observations might lead to shortening of the interval between US examinations or extending the surveillance programs to all HIV co-infected patients, regardless of liver disease stage. Currently, the criteria for entering HIV co-infected patients into programs for HCC screening are the same as for mono-infected patients, i.e., based on the stage of liver disease as previously discussed.

22.2.4 Cirrhosis of Non-viral Etiology as Target

The incidence of HCC in cirrhosis caused by diseases other than viral hepatitis is—with some exceptions—poorly defined. Chronic consumption of more than 80 g of ethanol per day for more than 10 years increases the risk for HCC by approximately fivefold, not to forget, however, that alcohol consumption of 10 g/day in women is associated with a 24 % increase of HCC risk [78]. Alcohol abuse in patients with chronic hepatitis C doubles the risk for HCC as compared with the risk in teetotaler carriers of HCV, since there may be a synergism between alcohol and hepatitis C in anticipating HCC onset or causing more severe histological pattern of tumor [79]. In a HCC cohort in Austria, alcoholic liver disease was the likely cause of HCC in 35 % of subjects [10], whereas in the United States, the hospitalization rate for HCC-related to alcoholic cirrhosis is 8–9/100,000/year compared to about 7/100,000/year for hepatitis C [11]. Altogether, this data indicates patients with alcoholic liver disease to warrant surveillance for HCC, as recommended by AASLD [8]. However, this may not be the case in other geographical areas like northern European countries where mortality in alcoholics is mainly related to acute on chronic liver failure rather than to HCC, a fact that discourages surveillance of cirrhotic alcoholics in terms of cost-effectiveness [80].

In the last two decades NASH has been increasingly recognized as a cause of cirrhosis and HCC, whereby many patients can progress to liver cancer without histological evidence of advanced fibrosis or cirrhosis [81, 82]. A recent analysis of patients referred for liver transplant evaluation at Clifford Hospital demonstrated a yearly cumulative incidence of HCC in 2.6 % of patients with NASH compared to 4.0 % of those with HCV over a median follow-up time of 3.2 years [83]. Older age at the time of cirrhosis diagnosis and any alcohol consumption were independently associated with the development of HCC in NASH-cirrhosis population, suggesting that alcohol intake, even in socially accepted amounts, may potentially increase the risk of HCC development both in NASH- and HCV-cirrhotic patients.

Findings from a SEER based reanalysis, suggested that diabetes is an independent risk factor for HCC being associated with a two- to threefold increase in the risk of HCC, regardless of the presence of other major HCC risk factors [14]. In parallel, a case control study in Italy provided further evidence that obesity and diabetes are either jointly or independently associated with an increased risk of HCC, likely accounting for a relevant number of HCC cases among subjects lacking markers of HBV/HCV infection [84]. Several large-scale epidemiological studies have associated the increasingly overweight prevalence and obesity among the general population with a higher risk of HCC [85, 86]. In a cohort of 900,000 American adults, the risk of dying from liver cancer was 4.5 times higher in men with a body mass index of 35 kg/m^2 or above compared to the reference group with a normal body mass index (18.5–24.9 kg/m^2) [85]. A meta-analysis of case control and cohort studies concluded that the relative risk of liver cancer was 1.17 for overweight subjects and 1.89 for the obese patients [87]. Major systemic and liver-specific molecular mechanisms like insulin resistance, hyperinsulinemia, increased tumor necrosis factor signaling pathways, and lipotoxicity all together drive the development of HCC in this set of metabolic diseases. As a matter of fact, both metformin and PPAR (Peroxisome proliferator-activated receptor)-gamma agonists that are active components of oral treatment of diabetes, have been associated with lower risk and improved prognosis of HCC [88]. Notwithstanding the benefits of surveillance in non-cirrhotic patients with NASH have been questioned by AASLD [8]. Conversely, surveillance is recommended by AASLD in patients with other metabolic diseases like cirrhotic patients with genetic hemochromatosis who have a 20-fold relative risk developing HCC, with an annual incidence of about 3–4 % [89, 90] or patients with stage-4 primary biliary cirrhosis who have about the same incidence of HCC as HCV-cirrhotics [91]. The incidence of HCC in autoimmune hepatitis with cirrhosis is quite low (about 1.1 %/year), not quite making the cut-off of 1.5 % at which HCC surveillance becomes cost-effective [92]. No recommendation was therefore made regarding surveillance in this group and in patients with alpha 1-antitrypsin deficiency, for whom there are insufficient data to accurately assess HCC incidence [93, 94].

22.2.5 Patients on the Liver Transplant Waiting List

Surveillance is endorsed by both AASLD and EASL for Child-Pugh C patients on transplant waiting list with the aim to early detect and manage tumor progression and to help defining priority policies for transplantation.

22.3 Screening Strategy

AASLD, EASL, and APASL share common recommendations for the semiannual surveillance with US of all patients at risk [8, 20, 21]. The choice of APASL of adding AFP as a screening test is not shared by the other associations which consider AFP of inadequate sensitivity and specificity for effective surveillance of HCC and the many small HCCs that do not secrete AFP [95–97]. Indeed, a few early tumors present with abnormal AFP serum levels, including those with the molecular signature of aggressiveness like tumors expressing the epithelial cell adhesion molecule EpCAM [90, 98, 99]. Another important reason for dropping AFP as a surveillance test is the lack of a standardized recall policy for patients without a liver node who have an abnormal AFP test. Finally, cholangiocarcinoma, the second most common primary liver cancer, with a completely different management and prognosis than HCC, may secrete AFP too [91, 92]. However, AFP could maintain a role in the surveillance of selected populations, one above all HBV patients under suppression with nucleotide analogs where confounding due to hepatitis flares is eliminated by effective antiviral therapy (Lampertico et al., unpublished observations).

Alternative serological markers of HCC like descarboxyprothrombin (DCP), glycosylated AFP (L3 fraction to total AFP, alpha fucosidase, glypican 3 (GPC-3), heat-shock protein 70 and DR-70 immunoassay have no added value as screening tests than AFP [100–115]. One possible exception is osteopontin that has been reported to be a more accurate predictor of HCC than AFP; however these observations need to be externally validated [116].

US is the most accurate and widely used test for surveillance. A small HCC on US may take on one of several different appearances, none of which is specific: the smallest lesions may be echogenic, because of the presence of fat in the tumor cells; other may be hypoechoic or show a “target like lesion” appearance. The US sensitivity is between 65 and 80 % with a specificity greater than 90 % when used as a screening test [117]. The widespread popularity of US relies on the absence of risks, non-invasiveness, good acceptance by patients, and relatively moderate cost [115–117]. However, the performance characteristics of US are not ideal in obese individuals with fatty liver disease and cirrhosis. This notwithstanding, US is superior to any serological test and no alternative strategy for surveillance has been adequately tested. Finally, combined use of AFP and US increases detection rate by 6–8 % only, however at the expenses of a substantial increase in costs (80 %) and false-positive rates. Indeed, the false-positive result rates that are 2.9 % for US and 5.0 % for AFP alone, reach 7.5 % for the combination [118].

At variance with AASLD, EASL and APASL, the Japanese Association of the Liver recommends intensified screening

every 3 or 4 months in men with viral cirrhosis or chronic viral hepatitis of increasing age, or with a history of alcohol abuse, since these patients are considered at very high risk of HCC [119]. However, the strategy of intensified screening contrasts with the paradigm that the intervals of screening are not dictated by the level of HCC risk, which may range from 1 to more than 3 % per year, but by the growth rate of the tumor only, which takes 6 months to double its volume, on average [3]. While it is crystal clear that intensified screening aims to identify liver cancer at the smallest size possible in order to optimize treatment, the effectiveness of this policy is largely questioned. In a recent study in France in patients with cirrhosis (mostly alcoholic) who were randomly allocated to standard (6 months) versus intensified (3 months) intervals of screening for HCC [120], during a median period of 47 months the 2 groups of study showed similar rates of cumulative 5-year incidence of HCC nodules (10.0 % vs. 12.3 %), cumulative incidence of HCC $\leq$ 20 mm and 30 mm in diameter, access to curative treatments (62 % vs. 58 %) and liver-related mortality (85 % vs. 86 %). However, the fact that the 5-year cumulative incidence of liver nodules was higher in the 3-month arm (41 % vs. 28 %), clearly heralds a greater economic burden to reach a final diagnosis, which might negatively impact on morbidity and cost utility ratio of intensified screening.

22.4 The Recall Policy

Recall policies consist of a defined algorithm to be activated whenever a surveillance test shows an abnormal result. Any nodule not seen on a prior study should be considered abnormal as an enlarging or changing echo pattern mass, even if previously considered to be benign. The nodular cirrhotic liver poses problems in US interpretation because early HCC can be difficult to distinguish from background nodularity. While a number of cirrhotic nodules can be as large as 2 cm, the majority of nodules smaller than 1 cm are not HCC [121]. Recall is intimately intertwined with the process of making a diagnosis. An accepted rule is to consider any small nodule as an abnormal screening result warranting further investigation [18]. These new nodules should trigger the recall strategy for diagnosis with either non-invasive or invasive (biopsy) criteria. According to both AASLD and EASL guidelines, cirrhotic patients and patients with chronic hepatitis B with a nodule less than 1 cm in diameter detected by US should receive an US examination every 4 months the first year and every 6 months thereafter, until the nodule grows to the point to be diagnosed by either non-invasive criteria or biopsy (Fig. 22.1). CT scan and magnetic resonance imaging (MRI) serve the purpose to demonstrate early arterial enhancement of the nodule and washout of contrast in the portal/venous and delayed phases of the exam [122], which are the radiological hallmarks of HCC. Since US microbubbles are confined to the intravascular space as opposed to iodinated contrast-CT or gadolinium-based MR imaging, where contrast agents are rapidly cleared from the blood pool into the extracellular space, contrast enhancement US (CEUS) may increase the rate of false-positive diagnosis of HCC in patients with an intrahepatic cholangiocarcinoma (ICC), without serving as a staging technique. Thus, CEUS has been dropped from the diagnostic algorithm of HCC endorsed by AASLD and EASL. Along this line, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) which suggested the typical enhanced pattern for ICC to be a rim-like enhancement (or non-enhancement)

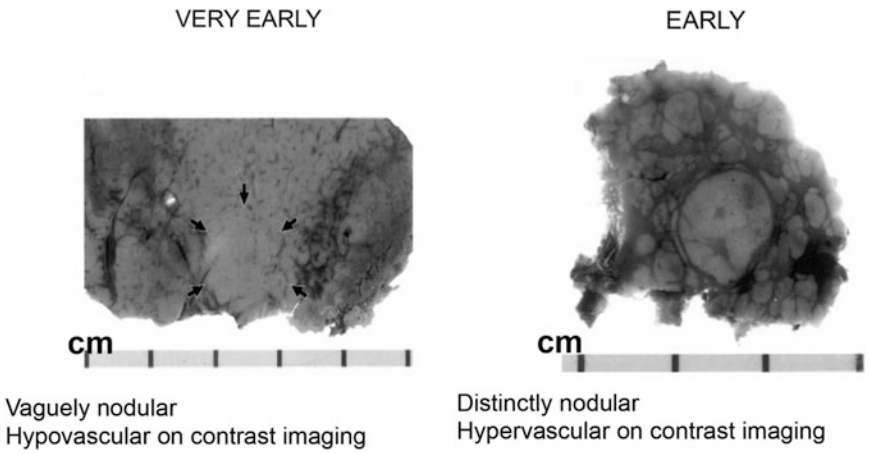

Fig. 22.1 Very early versus early: 5-year survival after resection of 93 % versus 54 %. According to both AASLD and EASL guidelines, cirrhotic patients and patients with chronic hepatitis B with a nodule less than 1 cm in diameter detected by US should receive an US examination every 4 months the first year and every 6 months thereafter, until the nodule grows to the point to be diagnosed by either non-invasive criteria or biopsy. Very early HCC has an indistinct nodular pattern, escapes detection with contrast imaging and has a better prognosis than early HCC. Permission from Elsevier

during the arterial phase followed by hypo/non-enhancement during the portal and delayed phases [123] and APASL endorse dynamic MRI and CEUS for the diagnosis of HCC. Nodular lesions showing an atypical imaging pattern, such as iso- or hypo-vascular in the arterial phase or arterial hypervascularity alone without portal-venous washout, can be better diagnosed by Sonazoid- or Levovist-enhanced US (a second generation contrast enhanced US) and/or SPIO-enhanced MRI to investigate the hepatospecific pattern of the nodules [22].

The AASLD algorithm for investigating nodules between 1 and 2 cm endorses the sequential use of a single imaging technique demonstrating the radiological hallmark of HCC, which has been demonstrated to reduce the need for FNB procedures for the final diagnosis of HCC, without affecting the sensitivity and specificity rates of the recall policy [124–126] (Fig. 22.2). However, the radiological diagnosis of HCC is frequently challenged by false-positive results generated by artero-venous shunts and macroregenerative nodules with dysplastic liver cells. In a retrospective study conducted by Yu et al. [127] in cirrhotic patients with a liver nodule who underwent liver transplant a specificity of 96 and 87 % was found for CT and MRI, respectively, with false-positive imaging results including macroregenerative or dysplastic nodules and non-hepatocellular neoplasms like intrahepatic cholangiocarcinoma (ICC). A lower specificity rate of both imaging techniques was reported in a prospective study of patients under surveillance; because the "typical" vascular pattern was seen in the whole set of high grade dysplastic nodules, whereas a majority of these nodules rapidly progressed toward HCC during the follow-up, outlining the importance of a prompt identification and treatment [128]. Patients with a radiologically undiagnosed liver nodule are indicated to a US guided liver biopsy, which in many instances will disclose the presence of grade-1 HCC endowed with the best prognosis [129]. The strategy of

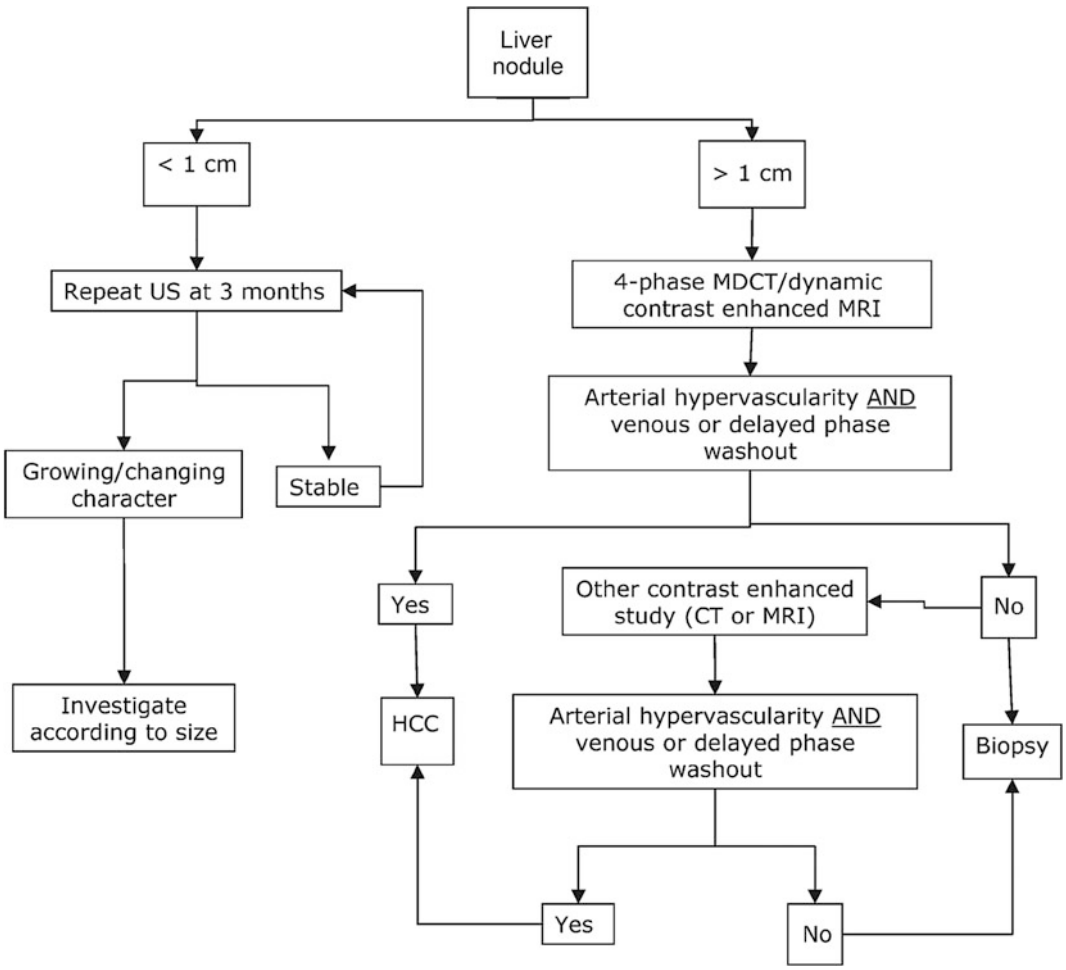

Fig. 22.2 Algorithm for investigation of small nodules found on surveillance in patients at risk for hepatocellular carcinoma [8]. The AASLD algorithm for investigating nodules between 1 and 2 cm endorses the sequential use of a single imaging technique demonstrating the radiological hallmark of HCC, which has been demonstrated to reduce the need for FNB procedures for the final diagnosis of HCC, without affecting the sensitivity and specificity rates of the recall policy. AASLD 2010; Bruix and Sherman. Management of Hepatocellular carcinoma: an update. Hepatology 2011. Permission from Elsevier

Table 22.2 The Importance of Liver Biopsy to Discriminate HGDN from Early HCC

Diagnostic approach		Etiology	HGDN versus HCC	Reference
Histology	Reticulin	HBV/HCV	Stromal invasion (−) versus (+)	Kojiro et al. [132]
Immunostatin	GPC3, HSP70, GS, CHC	Mixed	At least 2: 50 % sens. 100 % spec.	Di Tommaso et al. [133]
PCR	13 genes	Mixed	98 % accuracy	Paradis et al. [134]
	GPC-3 survivin LYVE-1	HCV	94 % accuracy	Llovet et al. [135]
Microarray	120 genes	HBV	100 % accuracy	Nam et al. [136]
	93 genes	HCV	100 % accuracy	Wurmbach et al. [137]

restricting a liver biopsy only to hyper-enhanced nodules or in the presence of synchronous typical HCC to improve the cost utility ratio of screening is questioned by many [130]. Undoubtedly, nodules not diagnosed by radiology require a tight follow-up every 4 months as well as a second biopsy. The risk of seeding should be considered before performing a liver biopsy: in 41 papers specifying the total number of patients biopsied, the median risk of seeding was 2.9 % (range 0–11 %), being lower (0.61–1.4 %) in patients undergoing therapeutic percutaneous procedures [131]. The importance of a liver biopsy rests on its ability to discriminate between HCC and dysplastic macronodules by the exclusion of microscopic stromal invasion [132] (Table 22.2). Immunostaining for GPC-3, and structural and functional analysis of the genetic profile of the nodules may also distinguish between macronodules and HCC but all these approaches likely work better in resected nodules than in tissue cores obtained through a liver biopsy [132]. Immunohistochemistry of more markers may serve the purpose to differentiate HCC from dysplastic nodules, like staining for clathryn heavy chain (CHC) used in addition to HSP70, GPC3 and GS despite the fact that pre-test probability of HCC diagnosis is already high in the set of focal lesions where it was detected [133]. Falsely negative nodules at contrast imaging may account for approximately 20 % of all 1–2 cm in size HCCs [138].

22.5 Efficacy of Surveillance

Surveillance aims to detect small HCCs that are amenable to receive curative treatments, resulting in a significant reduction in liver-specific mortality compared to patients carrying a symptomatic HCC [139–143]. In a meta-analysis of 23 studies in patients with cirrhosis, surveillance for HCC resulted in a 19 % reduction of 3-year mortality [142]. In a retrospective cohort study of 680 patients with a HCC in Taiwan, the receipt of routine or opportunistic (for incidental or non-hepatic purposes) US was associated with a 63 % reduction in mortality compared to the diagnosis of a symptomatic tumor [143]. In the last decade, more than 50 % of all patients in Japan have been diagnosed with a TNM I/II tumor compared to the 1980s, when <10 % of the patients with a HCC was diagnosed at an early stage [144]. In Alaska, a surveillance program of semiannual determinations of serum AFP in HBV carriers led to the identification of curable HCC in 40 % of the affected population, a fact that was perceived as beneficial since prior to AFP screening program the case-fatality rate for HCC in Alaskan natives was 100 %, with an average survival of 3 months only [145]. A randomized controlled study in Shanghai using abdominal US and serum AFP every 6 months to screen individuals with chronic hepatitis and other risks for HCC showed a reduction of the mortality rates in screened versus unscreened population of 83.2 versus 131.5 per 100,000 inhabitants [146]. However, the proportion of patients with cirrhosis was unknown, transplantation was not included among the radical therapies and the compliance of the population to the program was suboptimal (58 %). Notwithstanding all these limitations, the Shanghai study is the only randomized controlled trial to confirm the importance of early diagnosis for improving HCC-related mortality. In Milan, a reanalysis of 112 cirrhotic patients with a HCC detected during a hospital-based surveillance program showed the survival rates to be improved in patients who were treated for a liver cancer detected during the last 5 years of surveillance compared to previous intervals (90 % vs. 55 %, $p = 0.0009$) [147]. Increased survival was attributed to a significant reduction in the mortality rates of treated patients (from 34 to 5 %, $p = 0.003$), due to wider application of curative treatments and improved selection of patients undergoing surgical or ablative treatments. In Taiwan between 1989 and 1998, there was a significant increase in survival among 3345 patients with a HCC during the last 5 years (from 29 to 35 %), that was only in part (34 %) due to advancement in medical care, but mostly (66 %) attributable to early detection [148].

The positive results reported by these observational studies must be interpreted in the context of almost unavoidable potential biases such as lead time bias, i.e., the apparent improved survival that comes from the diagnosis being made earlier in the course of a disease than when the disease is diagnosed because of the development of symptoms or length bias, i.e., the apparent improvement in

survival that occurs because surveillance preferentially detects slow growing and better treatable cancers.

These potential biases notwithstanding, surveillance for HCC is considered a standard of care, not a clinical option. This is clearly perceived by majority of informed patients who believe surveillance to be the only practical approach to improve prognosis of HCC as reported by a survey in cirrhotic patients carried out in three academic centers in Sidney, Australia, who were asked to enter a randomized control trial of surveillance for HCC [149]. Despite appreciating the relevance of a randomized controlled study to determine the applicability, efficacy, and cost-effectiveness of HCC screening, the vast majority of informed responders (98 %) preferred surveillance. One reason for declining randomization is fear of the arbitrary nature of the process and also patients desire to have a more active role in medical decision-making, suggesting that a randomized controlled study of HCC surveillance is nowadays unfeasible in informed patients with a disease like cirrhosis known to predispose to liver cancer. Apparently, cost-effectiveness of screening was less than an issue among patients than it was among physicians, yet most of them (74 %) reported to routinely screen all cirrhotic patients. This contrasts with a population-based study in the USA where 6.6 % of 3903 Medicare patients with HCC were shown to receive regular surveillance prior to diagnosis, only [6], a finding which replicates the low rate of screening uptake (12 %) among hepatitis C infected veterans with cirrhosis [7]. Interestingly, the fact that gastroenterologists, hepatologists, or physicians with an academic affiliation were more likely to perform surveillance than practitioners involved in community-based practices suggests that barriers to screening like limited or outdated knowledge, lack of financial incentives, limited access to appropriate testing and treatment, altogether work against screening effectiveness.

Thus, despite benefits of surveillance for HCC are appreciated by most physicians and patients, surveillance for HCC is not a consolidated practice as it should, even in resource-rich countries. To bridge the chasm of screening for HCC, educational programs advocating screening in risk populations should be implemented targeting both patients and stakeholders in the field, while waiting for a breakthrough in the strategy of screening to occur, which may lead to a switch of screening programs from hospitals to the community, with the aim to improve population's access.

22.6 The Economic Consequences of Surveillance

While the benefits are intuitive, the economic consequences of HCC surveillance strategies are generally poorly appreciated, due to the lack of randomized trials evaluating moderators of treatment outcome like compliance, heterogeneity of liver disease and treatment effectiveness that, in addition to tumor incidence, impact on cost–utility ratio of surveillance. The never-ending argument of cost–utility ratio of surveillance has been analyzed by Markov modeling; moreover in the frame of epidemiological and interventional assumptions which do not necessarily reflect real-life practices. This further underscores the chasm between efficacy and effectiveness of screening for HCC, which may also be inflated by a priori decision to measure cost–utility ratios at less than US$50,000 for quality adjusted life year (QALY) saved. This assumption may conflict with policies of equitability while being influenced by the trends of economy, worldwide [150]. The review and economic analysis published by Coon et al. [151] modeled a population with a diagnosis of compensated cirrhosis who were also eligible to enter a surveillance program. Based on the assumptions used in the model, the most effective surveillance strategy uses a combination of AFP testing and ultrasound at 6-month intervals. Compared with no surveillance, this strategy is estimated to more than triple the number of people with operable HCC tumors at time of diagnosis, and almost half the number who die from HCC. This is a result of the identification of over ten times as many small HCC tumors (less than 2 cm in diameter) and over twice as many medium-sized tumors (between 2 and 5 cm in diameter). Consequently, more tumors are suitable for surgical intervention. Under the conditions of the model, this surveillance strategy would lead to an increase in the percentage of liver transplantations performed for known HCC (as opposed to decompensated cirrhosis) from 8 to 28 %, compared with no surveillance. A cost–utility analysis done in parallel indicates that adding US to 6-month AFP surveillance led to a cost–utility ratio of US$60,000 for QALY gained. Surveillance appeared to be more cost-effective in individuals with hepatitis B-related cirrhosis, potentially due to the younger age at diagnosis of cirrhosis.

22.6.1 How to Optimize Surveillance?

To improve cost-effectiveness of HCC screening, strengthening prediction at individual level through pre-treatment patient stratification by clinical or histological scores has been attempted, yet with uncertain benefits. In a study in Spain, 463 patients were prospectively and randomly included in a program for early diagnosis of HCC [152] based on abdominal US and measurement of AFP levels every 3 or 6 months. In the multivariate analysis, development of HCC was predicted by age 55 years or older, anti-HCV positivity, prothrombin activity 75 % or less, and platelet count less than $75 \times 103/mm^3$. Using these variables to construct a clinical-biological predictive score, two

groups of patients at low (2.3 %) and high risk (30.1 %) of developing HCC in 4 years, were identified.

22.6.1.1 Viremic Patients

Based on a mix of demographic, virological, and clinical features, propensity scores were generated in the NUC era in patients with chronic hepatitis B and therefore they could be used to optimize selection of screenees in HBV hyperendemic areas.

These scores, however, differ from each other in terms of applicability in real life, since REACH-B [153] stands as the only score developed in a community of non-cirrhotic population; conversely, GAG [154] and CU-HCC [155] were obtained in hospital patients, both including the diagnosis of cirrhosis, but only REACH-B and CU-HCC were externally validated.

From a clinical standpoint the three scores shared the merit to accurately identify patients who had remained HCC-free during a surveillance period of 3 years (NPV of 98 %), suggesting their safe use as negative predictors to optimize surveillance programs in an hyperendemic area like China. However, when REACH-B was tested in patients with cirrhosis in the validation study, its prognostic accuracy resulted affected. To overcome the burden of cirrhosis diagnosis, liver stiffness measured by fibroscan was incorporated in CU-HCC, leading to 100 % negative predictive power of the score in a 3-year surveillance period [156]. Unfortunately, all these scores did not optimally perform in non-Chinese populations: when applied to a North American population with HBV, REACH-B was the only model to show a robust negative predictive value for HCC during the first years of surveillance [157].

As expected, risk scores for HCC have been developed in patients with chronic hepatitis C, as well. A score based on age, gender, platelets and AFP was developed more than 10 years ago in Japanese patients with HCV-related cirrhosis and externally validated, providing a frame for stratifying patients into very low, intermediate and high risk groups of developing cancer in a 5 and 10 year period [158]. Unfortunately, the lack of a robust negative predictive power renders this propensity score unfit for optimizing patient selection for screening programs whereas the level of risk does not predict the growth rate of HCC, which in fact is the only parameter to dictate the optimal intervals of screening. More recently, a score has been developed and validated using the REVEAL cohort of asymptomatic anti-HCV subjects in Taiwan, which combines age with laboratory and virology features and diagnosis of cirrhosis [159]. The score succeeded in stratifying subjects in three risk levels independently on viremia, however with an unacceptable 5 % risk of developing HCC in the low risk category. Other scores based on demography, portal hypertension and AFP have been developed in patients with chronic hepatitis C, yet without any external validation, and for this reasons these scores cannot be considered for real-life practice.

22.6.1.2 Non-viremic Patients

Since antiviral therapy does not eliminate the risk of HCC in patients who are chronically infected with HBV while it is an important HCC risk modifier, propensity scores validated in viremic patients need to be separately evaluated in patients with NUC-suppressed viremia to see whether they maintain a robust prediction power, too.

In a comparative study by Wong and associated, all three propensity scores developed in Asia did perform as negative predictors of HCC as they did in viremic patients. In addition, patients with improved GAG and CU-HCC at year two of entecavir therapy had a 50 % reduced risk of developing a HCC during the same time period [160]. This is an important data to refine strategies of surveillance, considering that HCC can only be prevented in two-thirds of patients undergoing 5 years of NUC therapy who were aligned by these scores. In two studies in European patients, the performance of these three Chinese scores was suboptimal, likely consequence of the epidemiological differences existing between Caucasian and Chinese patients with HCC [161, 162]. While the importance of these propensity scores relies on their practicality, we should not forget that in HBV patients undergoing NUC therapy HCC was predicted by patient age, presence of cirrhosis, and diabetes mellitus, suggesting that development of liver cancer in virally infected populations is multifactorial [163]. In the Western world the retrospective analysis of 1666 patients who were long treated with NUCs showed an association between cancer risk and patient age, platelets and liver status. Combining patient age, gender, and platelet count it was possible to elaborate a propensity score named PAGE-B for Caucasian patients under NUC therapy whereby a group of patients with 0 risk of developing liver cancer in a 5-year period of surveillance, could be identified [164].

A propensity score has been developed also to predict HCC in patients with chronic hepatitis C who achieved an SVR to pegIFN based therapy. Using a score based on age, platelet count, AFP, and advanced fibrosis, Chang and co-workers were able to stratify patients into low risk, intermediate risk and high risk of developing liver cancer groups [69]. Unfortunately, the low risk group was burdened by 1.4 % residual risk of developing HCC over a 5-year period of surveillance, a fact that frankly discourages tuning of surveillance strategies by this predictive score system. However, the use of demographic and laboratory criteria makes this propensity score user-friendly and circumvents the need of detecting residual cirrhosis with either non-invasive or invasive procedures.

Currently, none of the propensity scores developed thus far in patients with chronic hepatitis B or C has been

enriched by genetic predictors of tumor susceptibility, possibly because none of studies based on genetic polymorphisms or molecular signatures could identify robust predictors for a molecularly heterogeneous cancer like HCC in at risk populations [165–167].

Propensity scores have been developed to assess HCC risk in both virus etiologies with the aim of optimizing intervals of screening in patients with a robust negative prediction of HCC in a short time period. While prediction is of overwhelming importance to optimize hospital-based surveillance programs with abdominal US, these findings raise the argument whether it can ethically be accepted to deny screening to patient at low risk of cancer therefore jeopardizing patient access to effective radical therapies. Moreover, there is an urgent need to identify HCC predictors in the general population, independently on liver disease etiology that would allow to bring screening for HCC from hospital-based facilities among the community. Such a switch of surveillance strategy might, in fact, improve patient access to screening, thereby resulting in greater survival benefits provided by expanding the number of patients identified with an early HCC.

22.7 Conclusions

A recent study in SEER-13 registries [1] highlighted the emergence of a bounce of epidemiological HCC-related encouraging findings, like the incidence rates of localized-stage HCC increasing faster than rates of regional- and distant-stage HCC combined (8 % vs. 4 % per year). The incidence rates of reported first-course surgery or tumor ablation increased faster than incidence rates of HCC without receiving such treatments (11 % vs. 7 %). Finally between 1975–1977 and 1998–2007, 5-year cause specific HCC survival increased from 3 to 18 %. While this data suggests that HCC survival is improving as a consequence of more patients being diagnosed and treated at early stages, additional progress may be possible through educational programs advocating screening in risk populations while waiting for a breakthrough in the strategy of surveillance to occur which leads to a switch of screening programs from hospitals to the community, with the aim to improve population's access. Finally, although survival benefits of screening are not evidence based, surveillance of patients at risk stands as the only practical approach to reduce HCC-related mortality owing to the remarkable improvement of treatment outcome in patients with early detected tumors compared to those with late discovered, incidental tumors.

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