

## Role of Surveillance in Hepatocellular Carcinoma

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### Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver tumour with rising incidence and has significant mortality of over 600,000 deaths annually. HCC is ranked as the third-leading cause of cancer-related deaths worldwide. An important feature is its unique geographic distribution due to the associated risk factors related to the tumour. Surveillance programmes are recommended in the specified targeted population and help in early diagnosis of HCC with timely therapeutic intervention.

Success of surveillance depends on multitude of factors including identification of the target population, proper use of surveillance tests through a structured programme and this in turn leading to proper management of HCC. The most important risk factor associated with HCC is hepatic cirrhosis. Important factors in the aetiology of cirrhosis include chronic infection from hepatitis B (HBV) and C (HCV) viruses and alcohol abuse. Another risk factor increasingly being recognised is non-alcoholic fatty liver disease. Radiological and serological investigations are employed in the screening and surveillance of HCC. Debatable issues in this regard include surveillance interval, efficacy of tests, outcomes of detected tumours and proper recall guidelines which are considered as important factors for success of surveillance programmes. Ultrasonography is considered as the most reliable test modality in surveillance programmes.

**Keywords:** Hepatocellular carcinoma; Viral hepatitis; Surveillance; Cirrhosis; Target population; Ultrasonography; Alpha fetoprotein

### Introduction

Surveillance being an important tool in the management of medical conditions consists of the periodic application of a diagnostic test to a set of defined population at risk for developing a given disease. Factors which influence the outcomes of surveillance programmes include the incidence of the surveyed disease in the target population, the availability of efficient diagnostic tests at acceptable cost and their feasibility for the target population. Post detection follow up with availability of therapeutic modalities enhances effectiveness of such programmes [1].

Reduction in disease related mortality is the main aim of surveillance which is achieved through an early diagnosis (stage migration) that, in turn, enhances the applicability and cost-effectiveness of curative therapies. Stage migration, however, cannot serve as a surrogate marker for the main end-point, which is patient survival. Identification of viral hepatitis and other liver conditions leading to cirrhosis helps in defining target population for surveillance. In the Western world, HCC arises in a cirrhotic liver in up to 90% of cases and cirrhosis being a progressive disease also affects patient survival [2]. Presence of cirrhosis influences the chance of success for anti-tumour treatment modalities and affects their outcome; it renders early diagnosis of HCC even more crucial in the management plan. Moreover, many available treatments can have a detrimental impact on cirrhosis. This means that the cause of mortality cannot be clearly defined as to the underlying disease or HCC and in this context a reduction in overall mortality will represent a more appropriate end-point to assess the efficacy of surveillance. This review focuses on various aspects of HCC surveillance including identification of target population and proper use of available tests.

### Target Population for HCC Surveillance

Hepatocellular carcinoma (HCC) is a highly prevalent tumour. The most relevant risk factors for HCC which are well described include chronic hepatitis C (HCV) infection, hepatitis B (HBV) infection, alcoholic cirrhosis, and non-alcoholic steatohepatitis. Additionally, the increasing incidence of obesity and diabetes, which have also been identified as independent risk factors for chronic liver disease and HCC, is likely to further augment the number of

Americans afflicted with HCC [3-5]. Table 1 includes patient groups suitable for surveillance.

The rising incidence of tumour in the Western countries and United States is mainly attributed to the current HCV epidemic and the burden of HCV related HCC is thus expected to continue to increase over the next two decades [6]. This dramatic increase in HCC is driven by the epidemic of HCV that peaked in the 1980s and the 20-30 year lag time in its natural history between the onset of infection and the development of cirrhosis. However, the overriding risk factor in 80-90% of HCC regardless of aetiology is the presence of cirrhosis [7,8]. There is a clear association of HCC with underlying cirrhosis and its annual incidence in cirrhotic patients is in the range of 3-5% with around one-third of individuals developing HCC during their lifetime [9]. Therapeutic modalities including surgical resection and liver transplantation offer

Individuals with cirrhosis	Individuals without cirrhosis
Viral infections 1- Hepatitis B 2- Hepatitis C	Hepatitis B carrier 1- With family history of HCC 2- African over 20 years 3- Asian male over 40 years 4- Asian females over 50 years
Alcohol	
Genetic conditions 1- Hemochromatosis 2- Alpha-1 antitrypsin deficiency	
Other 1- Primary biliary cirrhosis 2- Fatty liver (steatosis)	

**Table 1:** Candidate population at risk for HCC and target for surveillance.

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the best potential for cure in HCC. Success however depends on an early detection of tumour which currently is only achieved in 10-20% of cases [10]. This means that majority of patients are not suitable for curative therapies due to their advanced tumour stage at the time of diagnosis. Based on these facts, screening and surveillance strategies for HCC have been developed with the goal of detection at an earlier stage so that intervention strategy yields good results [11]. At the same time however, evidence in support of screening is not robust as it would be unethical to randomize at-risk patients into screened and nonscreened groups to compare outcomes. In an interesting randomised study, Zhang et al. compared surveillance and no surveillance in hepatitis B (HBV) patients using serum alpha-fetoprotein (AFP) and abdominal ultrasound at 6-month intervals [12]. Results of this study demonstrated the benefit of surveillance in terms of reduced mortality. Many other cohort studies have also strengthened this conclusion by showing a survival advantage for patients included in a surveillance programme while retrospective studies have demonstrated its cost-effectiveness [13-16].

### Cirrhotic Patients

Not all cirrhotic individuals have the same risk of developing HCC. In general terms a decision analysis and cost-effectiveness model will suggest that an intervention is considered cost-effective if it provides gains of life expectancy of at least 3 months with a cost lower than approximately US\$ 50,000 per year of life saved [17]. Cost-effectiveness studies indicate that an incidence of 1.5%/year or greater would warrant surveillance of HCC in cirrhotic patients irrespective of its aetiology [18-21]. On one hand it may be possible to identify cirrhotic patients at low risk of developing HCC and hence exclude them from surveillance, thereby saving costs although this approach is not proven yet [9,22,23]. On the other hand, the presence of advanced cirrhosis (Child-Pugh class C) prevents potentially curative therapies from being employed, and thus surveillance is not cost-effective in those individuals [24,25]. One significant exception is patients on the waiting list for liver transplantation, regardless of the hepatic functional status and they should be screened for HCC in order to detect tumours exceeding conventional criteria to help define priority policies for transplantation. Although it seems that surveillance might not be cost effective above a certain age cut-off, however, the lack of data prevents the adoption of any specific recommendation.

### Non-Cirrhotic Subjects

Individuals who have chronic HBV infection are at a risk of HCC development even in the absence of cirrhosis. In these cases, the recommended cut-off of annual incidence above which surveillance should be recommended cannot be applied. The cut-off of annual incidence in these patients is ill-defined, albeit expert opinion indicates that it would be warranted if HCC incidence is at least 0.2%/year [26,27]. Thus, cost-benefit modelling needs to be considered in this scenario. Current available data suggests that the incidence of HCC in adult Asian or African active HBV carriers or with a family history of HCC exceeds this value, whereas HCC incidence ranges from 0.1% to 0.4%/year in Western populations with chronic HBV infection [28,29].

In individuals with HBV infection another important risk factor is viral load which appears to increase the risk of developing HCC. For Asian patients, serum HBV-DNA above 10,000 copies/ml was associated with an annual risk above 0.2%/year [29]. There is scanty and sometimes contradictory information on the incidence of HCC in patients with chronic hepatitis C without cirrhosis. Data from Japan would suggest that patients with mild fibrosis have a yearly HCC incidence of 0.4%

[30]. Similar results were reported from United States and HCC risk was higher in patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis (Metavir F3) [31]. The fact that the transition from advanced fibrosis and cirrhosis cannot be accurately defined led the EASL guidelines to recommend surveillance also for patients with bridging fibrosis [26]. This panel also recommends such surveillance policy. In this regard, transient elastography appears to be a promising tool with ability to stratify patients at different HCC risks [32].

With the current available data the incidence of HCC in patients with nonviral chronic liver disease without cirrhosis, such as non-alcoholic and alcoholic steatohepatitis, autoimmune liver disease, genetic hemochromatosis,  $\alpha$ 1-antitrypsin deficiency, and Wilson disease remains largely unknown [33]. However, available evidence suggests that HCC usually arises in these contexts once cirrhosis is established [1]. It is advisable that patients with metabolic syndrome or non-alcoholic steatohepatitis leading to cirrhosis should also undergo surveillance; however the risk of HCC development is not fully established in non-cirrhotic individuals [34].

### Treated Viral Chronic Hepatitis

An interesting development relates to the recent advances in anti-viral therapies which have led to relatively high rates of viral clearance or suppression among patients being treated for chronic hepatitis B or C. Successful treatment, leading to sustained virological response in chronic hepatitis C, and HBeAg seroconversion or sustained HBV-DNA suppression in chronic hepatitis B, decreases, but does not eliminate the risk of HCC [35-38]. A safe approach will be to offer surveillance to treated patients with chronic hepatitis B if they remain at risk of HCC development due to baseline factors, and to those with HCV-induced advanced fibrosis or cirrhosis, even after achieving sustained virological response.

### Surveillance Tests

HCC surveillance is mainly based on two types of tests including serological and imaging examinations. While using any surveillance test it is important that test is validated for accuracy and has reasonable predictive value. An important additional consideration is that the natural history of sub-clinical HCC is not the same as for clinical cancer. In particular growth rates of sub-clinical HCC may be very different than tumour growth rates in clinically observed cancers. Second, sub-clinical cancer may not progress to clinically detectable cancer in all cases. Thus it cannot be assumed that all sub-clinical lesions found on surveillance will ultimately develop into cancer. Similarly, the performance characteristics of a test used to diagnose sub-clinical disease (i.e., as a screening test) are not the same as when the test is used for diagnosis. Therefore one cannot take the performance characteristics of a test used in diagnosis (e.g., CT scan) and extrapolate the sensitivity and specificity to the surveillance situation.

### Radiological Tests in HCC Surveillance

The imaging test most widely used for surveillance is ultrasonography (US). The widespread popularity of US also relies on the absence of risks, non-invasiveness, good acceptance by patients and relatively moderate cost. Nonetheless, US detection of HCC on a cirrhotic background is a challenging issue. US has an acceptable diagnostic accuracy when used as a surveillance test (sensitivity ranging from 58% to 89%; specificity greater than 90%) [39,40]. A recent meta-analysis by Singal et al. which included 19 studies has demonstrated that US surveillance detected the majority of HCC tumours before they presented clinically, with a pooled sensitivity of 94%. However, US were less effective for detecting

early-stage HCC, with a sensitivity of only 63% [41]. It should be remembered that the performance characteristics of US have not been as well defined in nodular cirrhotic livers undergoing surveillance [42-45].

Sato et al. in another study from Japanese cohort which included 1432 patients showed that careful US surveillance performed by highly skilled operators resulted in an average size of the detected tumours of  $1.6 \pm 0.6$  cm, with less than 2% of the cases exceeding 3 cm [46].

The most difficult ultrasounds are in obese individuals with fatty liver disease and cirrhosis. However, no alternative strategy for surveillance has been adequately tested. Some reports suggest the use of CT scanning as a screening test for HCC [47,48]. The performance characteristics of CT scanning have been developed in diagnostic/staging studies in which some other test has raised the suspicion of HCC. Thus, these results come from biased populations. The performance characteristics of CT scanning in HCC surveillance are unknown. In addition, for CT scanning to have maximum sensitivity this will require 4-phase scans, with the attendant high levels of radiation and potential long term carcinogenesis risk [49]. No recommendation can be made about CT scanning for individuals in whom visibility on ultrasound is inadequate. Ideally, ultrasonographers performing HCC surveillance should receive special training.

### Serological Tests in HCC Surveillance

Among the serological tests the performance characteristics of AFP have been studied extensively. Receiver operating curve analysis of AFP used as a diagnostic test suggests that a value of about 20 ng/mL provides the optimal balance between sensitivity and specificity [50]. However, at this level the sensitivity is only 60%, i.e., AFP surveillance would miss 40% of HCC if a value of 20 ng/mL is used as the trigger for further investigation. This is inadequately sensitive for general use. If a higher cut-off is used a progressively smaller proportion of HCC's will be detected. If the AFP cut-off is raised to, e.g., 200 ng/mL the sensitivity drops to 22%. Conversely, reducing the cut-off means that more HCC's would be identified, but at the cost of a progressive increase in the false-positive rate. This analysis was performed in a case control study where the prevalence of HCC was artificially set at 50%. At this prevalence the positive predictive value of an AFP of 20 ng/mL was 84.6%. However, if the HCC prevalence rates were more like those seen in most liver clinics, i.e., about 5%, the positive predictive value (PPV) of an AFP of 20 ng/mL is only 41.5%, and even at a cut-off of 400 ng/mL the PPV is only 60% [50]. In cohorts undergoing surveillance the incidence of HCC may be even lower than 5%, depending on the criteria for entry into surveillance. For example, in non-cirrhotic hepatitis B carriers infected in infancy the incidence of HCC is usually less than 1%. The lack of efficacy of AFP as a surveillance test has been confirmed recently as part of the HALT-C study [51]. In a prospective study Lok et al. [51] evaluated the efficacy of maintenance interferon and ribavirin for the treatment of patients with hepatitis C unresponsive to an initial standard course of therapy. These were all patients with cirrhosis, and over the period of the study HCC developed in 39 subjects. AFP and des-carboxy-prothrombin (DCP) were measured at intervals, so that measurements were available at the time of diagnosis and 12 months prior to diagnosis. These results clearly showed that both serological markers were inadequate for surveillance purposes, even when combined. Despite these facts the performance characteristics of AFP as a screening test remain inadequate.

It is important to remember that serum AFP has very poor sensitivity and specificity and should not be used as a screening tool in isolation unless ultrasonography (or other imaging modality) is

unavailable [52]. Diagnostic and surveillance potential for other serum biomarkers for early detection of HCC on the horizon such as des-gamma-carboxy prothrombin, the lectinbound AFP fraction (AFP-L3) and glypican 3 remain to be fully investigated [53]. Marrero et al. in a recent multicentre, phase 2 biomarker studies showed that AFP was more sensitive than DCP and AFP-L3 for the diagnosis of early-stage HCC at a cut-off of 10.9 ng/mL, this finding however needs further evaluation [54].

Other serological test investigated in HCC surveillance include DCP, also known as Prothrombin Induced by Vitamin K Absence II (PIVKA II) [55-58]. Most reports on the use of DCP have evaluated its use in a diagnostic mode, rather than for surveillance. There are reports of its use in a surveillance mode. However, as discussed above DCP is insufficiently accurate for routine use in surveillance. Another factor which fails to support its use as screening test is its use as a marker for portal vein invasion by tumour [59]. Results would also suggest that DCP is not a good screening test as tumour is only detected late in its course. In other words screening test should be able to identify early disease, not late disease. The HALT-C study also confirmed that DCP was not a good surveillance tool [60]. Other tests that have been reported as screening tests included the ratio of glycosylated AFP (L3 fraction) to total AFP, alpha fucosidase, glypican 3, and HSP-70 [61-74]. Use of these biochemical markers has not been adequately investigated and at this stage cannot be recommended as a screening or surveillance test. It is suggested that proteomic profiling may aid the development of more accurate markers [75].

### Miscellaneous Approaches in HCC Surveillance

Strategies such as alternating different surveillance modalities at intervals have no basis. The guiding principle should be that the best available screening test should be chosen, and it should be applied regularly. Combined use of AFP and ultrasonography increases detection rates, but also increases costs and false-positive rates [76]. AFP-only surveillance had a 5.0% false positive rate, ultrasound alone had a 2.9% false positive rate, but in combination the false positive rate was 7.5%. Ultrasound alone cost about \$2000 per tumour found, whereas the combination cost about \$3000 per tumour found. Cirrhosis is characterized by fibrous septa and regenerative nodules and these features produce a coarse pattern on US, which may impair identification of small tumours. Because of these limitations, the performance of US in early detection of HCC is highly dependent on the expertise of the operator and the quality of the equipment. The recent introduction of US contrast agents has not proven to increase the ability of US to detect small HCC tumours [77].

There are no data to support the use of multidetector CT or dynamic MR imaging for surveillance. Practical experience suggests that the rate of false-positive results that will trigger further investigation is very high and not cost-effective. In the setting of the waiting list for liver transplantation CT scan or MRI are alternatives to US. These techniques should be also considered when obesity, intestinal gas, and chest wall deformity prevent an adequate US assessment. Even in these circumstances, radiation risk due to repeated exposure to CT scan and high cost of MR make their use debatable in long-term surveillance.

### Surveillance Interval

The ideal interval of surveillance for HCC should be dictated by two main features including the rate of tumour growth up to the limit of its detection, and tumour incidence in the target population. Based on available knowledge on mean HCC volume doubling time, a 6-month interval represents a reasonable choice [78]. Considering

cases where inter-patient variability is huge, a shorter 3- month interval has been proposed by Japanese guidelines [79,80]. However, Nouse et al. in a randomized study comparing 3- versus 6-month based programmes failed to detect any differences [80]. On the other hand, cohort comparisons of 6 versus 12-month schemes provide similar results [81].

A surveillance interval of 6-12 months has been proposed based on tumour doubling times. The positive randomized control trial by Zhang et al. used a 6 month interval [82]. Based on retrospective study by Trevisani et al. one may question the benefit of screening as survival was no different in patients screened at 6 or 12 monthly intervals [83]. Another study by Santagostino et al. in HCV infected hemophiliacs suggested that the likelihood of finding HCC at the single nodule stage (as opposed to multinodular HCC) was the same with 6 and 12-month surveillance intervals [84]. These and other studies looking at surveillance intervals have used surrogate outcome markers, such a number of lesions, lesion size, or ability to provide potentially curative treatment. Most of these studies were in patients with hepatitis C. One (non-randomized) prospective cohort study by Kim et al. has evaluated survival (in patients with hepatitis B) and demonstrated that survival is improved with 6 months surveillance intervals compared to 12 months [85].

The decision to provide surveillance or not depends upon the magnitude of risk for HCC, but the surveillance interval is determined by the tumour growth rates and not by the degree of risk. In other words the surveillance interval need not be shortened for patients who are thought to be at higher risk. At the same time it is important to make the distinction between patients undergoing surveillance, i.e., those in whom although high risk is recognized, do not have any reason to suspect HCC, and those in whom surveillance tests have been abnormal and there is a concern that HCC is already present. Such patients are strictly speaking no longer candidates for surveillance, but should be receiving enhanced follow-up. Conversely, lengthening the surveillance interval for patients perceived to be a lower risk of HCC means that when an HCC develops it might be diagnosed at a later stage, thus possibly negating the benefits of surveillance. Meta-analysis of prospective studies by Singal et al. has shown that the pooled sensitivity of US-based surveillance decreases from 70% with the 6-month program to 50% with the annual programme [41]. Finally, cost-effectiveness studies have shown that 6 monthly US-based surveillance improves quality-adjusted life expectancy at a reasonable cost [86]. In light of available knowledge a 6-month scheduled surveillance appears the preferable choice. Further trials in this setting would be difficult to implement due to ethical issues.

## Surveillance Efficacy

Surveillance efficacy has been well documented in randomised trials. In a population-based study by Zhang et al. where cluster randomization was performed comparing surveillance (US and AFP measurements every 6 months) versus no surveillance in a population of Chinese patients with chronic hepatitis B infection, regardless of the presence of cirrhosis [12]. Although there was suboptimal adherence to the surveillance program (55%), HCC-related mortality was reduced by 37% in the surveillance arm as a result of increased applicability of resection in detected cases. The other AFP-based surveillance study carried out in Qidong (China) in high-risk individuals (males, HBsAg+) did not identify differences in overall survival [87]. Other types of evidence include population and non-population- based cohorts and cost-effectiveness analysis, which mostly reinforce the benefits of regular US schemes [79,84,88,89]. These studies can be criticised due to

their heterogeneous nature on account of variable disease stage, different aetiology of liver disease and used surveillance protocols. Additionally, almost all studies suffer from methodological biases such as lead-time bias (apparent improvement of survival due to an anticipated diagnosis) and length time bias (over-representation of slower-growing tumours). While the latter is unavoidable in this type of study, lead-time bias can be minimized using correction formulas. Application of corrections did demonstrate the advantage of surveillance [90].

## Recall Policies

Recall policies are the policies instituted to deal with an abnormal screening test result. This is different than surveillance. Recall policy is crucial for the success of surveillance programmes. It consists of a defined algorithm which needs to be followed when surveillance tests show an abnormal result. The tests are different, and the interval of follow-up is different. Recall policies cover the investigations and follow-up that determines whether an abnormality identified on surveillance is or is not HCC. Recall is intimately intertwined with the process of making a diagnosis. The first step is to define an abnormal result. Any nodule not seen on a prior study should be considered abnormal. A mass that enlarges is abnormal, even if previously considered to be benign. An obvious issue is with nodular cirrhotic liver which poses problems in ultrasound interpretation and early HCC can be difficult to distinguish from background nodularity. Some benign cirrhotic nodules can be as large as 2 cm; however, the majority of nodules smaller than 1 cm are not HCC [91].

## Clinical Practice Summary

The current American Association for the Study of Liver Diseases (AASLD) guidelines recommend HCC surveillance for high-risk groups such as all patients with cirrhosis and certain HBV-infected patients regardless of the presence of cirrhosis using an abdominal ultrasound at 6-12 month intervals [92]. Similar recommendations have been made by the European Association for the Study of the Liver (EASL) [93]. The ideal target of surveillance should be the identification of HCC at a very early stage (2 cm or less), as this gives the chance of commencing radical treatments and highest probability of long-term cure. In case of HCC, abnormal US results are either a newly detected focal lesion or a known hepatic lesion that enlarges and/or changes its echo pattern. In summary, recommendations in relation with surveillance and re-call policy should be followed to improve HCC outcomes in the following fashion.

## A-Surveillance

- 1- Patients at high risk for developing HCC should be entered into surveillance programs.
- 2- Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months.
- 3- A shorter follow-up interval (every 3-4 months) is recommended in the following cases:
  - a- Where a nodule of less than 1 cm has been detected (see recall policy)
  - b- In the follow-up strategy after resection or loco-regional therapies.
- 4- Patients on the waiting list for liver transplantation should be screened for HCC in order to detect and manage tumor progression and to help define priority policies for transplantation.

## B- Recall Policy

1. In cirrhotic patients, nodules less than 1 cm in diameter detected by ultrasound should be followed every 4 months for the first year and with regular follow up every 6 months thereafter.
2. In cirrhotic patients, diagnosis of HCC for nodules of 1-2 cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. It is recommended that biopsies are assessed by an expert hepatopathologist. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement pattern identified during follow-up.
3. In cirrhotic patients, nodules more than 2 cm in diameter can be diagnosed for HCC based on typical features on one imaging technique. In case of uncertainty or atypical radiological findings, diagnosis should be confirmed by biopsy.

## References

1. Prorok PC (1992) Epidemiologic approach for cancer screening. Problems in design and analysis of trials. *Am J Pediatr Hematol Oncol* 14: 117-128.
2. El-Serag HB (2011) Hepatocellular carcinoma. *N Engl J Med* 365: 1118-1127.
3. Veldt BJ, Chen W, Heathcote EJ, Wedemeyer H, Reichen J, et al. (2008) Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology* 47: 1856-1862.
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 348: 1625-1638.
5. El-Serag HB, Tran T, Everhart JE (2004) Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 126: 460-468.
6. Davis GL (1998) Impact of HCV infection: projections into the next century. *Hepatology* 28: 390A.
7. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, et al. (1993) Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 328: 1797-1801.
8. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA (2003) The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 139: 817-823.
9. Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, et al. (2004) Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology* 126: 1005-1014.
10. Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. *Lancet* 362: 1907-1917.
11. Collier J, Sherman M (1998) Screening for hepatocellular carcinoma. *Hepatology* 27: 273-278.
12. Zhang BH, Yang BH, Tang ZY (2004) Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 130: 417-422.
13. Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, et al. (1990) Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. *Hepatology* 12: 680-687.
14. McMahon BJ, Bulkow L, Harpster A, Snowball M, Lanier A, et al. (2000) Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. *Hepatology* 32: 842-846.
15. Wong LL, Limm WM, Severino R, Wong LM (2000) Improved survival with screening for hepatocellular carcinoma. *Liver Transpl* 6: 320-325.
16. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, et al. (2001) Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 48: 251-259.
17. Laupacis A, Feeny D, Detsky AS, Tugwell PX (1992) How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 146: 473-481.
18. Sarasin FP, Giostra E, Hadengue A (1996) Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. *Am J Med* 101: 422-434.
19. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, et al. (2006) The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. *Hepatology* 43: 1303-1310.
20. Fattovich G, Bortolotti F, Donato F (2008) Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 48: 335-352.
21. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, et al. (1999) Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHT Study Group. Inhibition of hepatocarcinogenesis by interferon therapy. *Ann Intern Med* 131: 174-181.
22. Ganne-Carrié N, Chastang C, Chapel F, Munz C, Pateron D, et al. (1996) Predictive score for the development of hepatocellular carcinoma and additional value of liver large cell dysplasia in Western patients with cirrhosis. *Hepatology* 23: 1112-1118.
23. Velázquez RF, Rodríguez M, Navascués CA, Linares A, Pérez R, et al. (2003) Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 37: 520-527.
24. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases (2005) Management of hepatocellular carcinoma. *Hepatology* 42: 1208-1236.
25. Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, et al. (2007) Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? *Am J Gastroenterol* 102: 2448-2457.
26. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, et al. (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 35: 421-430.
27. Di Bisceglie AM, Sterling RK, Chung RT, Everhart JE, Dienstag JL, et al. (2005) Serum alpha-fetoprotein levels in patients with advanced hepatitis C: results from the HALT-C Trial. *J Hepatol* 43: 434-441.
28. Sánchez-Tapias JM, Costa J, Mas A, Bruguera M, Rodés J (2002) Influence of hepatitis B virus genotype on the long-term outcome of chronic hepatitis B in western patients. *Gastroenterology* 123: 1848-1856.
29. Beasley RP, Hwang LY, Lin CC, Chien CS (1981) Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 2: 1129-1133.
30. Sakuma K, Saitoh N, Kasai M, Jitsukawa H, Yoshino I, et al. (1988) Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. *Hepatology* 8: 1642-1646.
31. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, et al. (2009) Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology* 136: 138-148.
32. Martínez SM, Crespo G, Navasa M, Forns X (2011) Noninvasive assessment of liver fibrosis. *Hepatology* 53: 325-335.
33. Bosch FX, Ribes J, Díaz M, Cléries R (2004) Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 127: S5-S16.
34. Yasui K, Hashimoto E, Komorizono Y, Koike K, Arai S, et al. (2011) Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 9: 428-433.
35. Craxi A, Cammà C (2005) Prevention of hepatocellular carcinoma. *Clin Liver Dis* 9: 329-346, viii.
36. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, et al. (2007) Italian Association of the Study of the Liver Disease (AISF). Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 45: 579-587.
37. Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL (2008) Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 28: 1067-1077.
38. Lampertico P, Viganò M, Manenti E, Iavarone M, Sablon E, et al. (2007) Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology* 133: 1445-1451.
39. Bolondi L (2003) Screening for hepatocellular carcinoma in cirrhosis. *J Hepatol* 39: 1076-1084.

40. Kim CK, Lim JH, Lee WJ (2001) Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver: accuracy of ultrasonography in transplant patients. *J Ultrasound Med* 20: 99-104.
41. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, et al. (2009) Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther* 30: 37-47.
42. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, et al. (2009) A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. *Gastroenterology* 137: 850-855.
43. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, et al. (2013) Resection of hepatocellular cancer 2 cm: results from two Western centers. *Hepatology* 57: 1426-1435.
44. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, et al. (2008) Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 47: 82-89.
45. Arai S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, et al. (2000) Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. *The Liver Cancer Study Group of Japan. Hepatology* 32: 1224-1229.
46. Sato T, Tateishi R, Yoshida H, Ohki T, Masuzaki R, et al. (2009) Ultrasound surveillance for early detection of hepatocellular carcinoma among patients with chronic hepatitis C. *Hepatology* 49: 544-550.
47. Di Tommaso L, Franchi G, Park YN, Fiamengo B, Destro A, et al. (2007) Diagnostic value of HSP70, glypican 3, and glutamine synthetase in hepatocellular nodules in cirrhosis. *Hepatology* 45: 725-734.
48. Paradis V, Degos F, Dargère D, Pham N, Belghiti J, et al. (2005) Identification of a new marker of hepatocellular carcinoma by serum protein profiling of patients with chronic liver diseases. *Hepatology* 41: 40-47.
49. Brenner DJ, Hall EJ (2007) Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 357: 2277-2284.
50. Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, et al. (2001) Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol* 34: 570-575.
51. Lok AS, Sterling RK, Everhart JE, Wright EC, Hoefs JC, et al. (2010) Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. *Gastroenterology* 138: 493-502.
52. Taketa K (1990) Alpha-fetoprotein: reevaluation in hepatology. *Hepatology* 12: 1420-1432.
53. Marrero JA (2005) Screening tests for hepatocellular carcinoma. *Clin Liver Dis* 9: 235-251.
54. Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, et al. (2009) Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology* 137: 110-118.
55. Llovet JM, Peña C, Shan M, Lathia C, Bruix J (2008) Biomarkers predicting outcome of patients with advanced hepatocellular carcinoma (HCC) randomized in the phase III SHARP trial. Presidential plenary session, AASLD 59th annual meeting, San Francisco. *Hepatology* 48: 372A.
56. Llovet JM, Bruix J (2003) Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 37: 429-442.
57. Vibert E, Azoulay D, Hoti E, Iacopinelli S, Samuel D, et al. (2010) Progression of alpha-fetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. *Am J Transplant* 10: 129-137.
58. Toso C, Trotter J, Wei A, Bigam DL, Shah S, et al. (2008) Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 14: 1107-1115.
59. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, et al. (2001) Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 91:561-569.
60. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst* 101: 1446-1452.
61. Riaz A, Kulik L, Lewandowski RJ, Ryu RK, Giakoumis Spear G, et al. (2009) Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. *Hepatology* 49:1185-1193.
62. Vora SR, Zheng H, Stadler ZK, Fuchs CS, Zhu AX (2009) Serum alpha-fetoprotein response as a surrogate for clinical outcome in patients receiving systemic therapy for advanced hepatocellular carcinoma. *Oncologist* 14: 717-725.
63. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, et al. (2010) editors. *AJCC Cancer Staging Handbook*. (7th edn). New York: Springer.
64. Sterling RK, Jeffers L, Gordon F, Sherman M, Venook AP, et al. (2007) Clinical utility of AFP-L3% measurement in North American patients with HCV-related cirrhosis. *Am J Gastroenterol* 102: 2196-2205.
65. Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, et al. (1999) A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. *J Hepatol* 31:133-141.
66. Villanueva A, Minguez B, Forner A, Reig M, Llovet JM (2010) Hepatocellular carcinoma: novel molecular approaches for diagnosis, prognosis, and therapy. *Annu Rev Med* 61: 317-328.
67. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, et al. (2001) Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 91: 561-569.
68. Wang M, Long RE, Comunale MA, Junaidi O, Marrero J, et al. (2009) Novel fucosylated biomarkers for the early detection of hepatocellular carcinoma. *Cancer Epidemiol Biomarkers Prev* 18: 1914-1921.
69. Leung TW, Tang AM, Zee B, Lau WY, Lai PB, et al. (2002) Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer* 94: 1760-1769.
70. Kitai S, Kudo M, Minami Y, Haji S, Osaki Y, et al. (2008) Validation of a new prognostic staging system for hepatocellular carcinoma: a comparison of the biomarker-combined Japan Integrated Staging Score, the conventional Japan Integrated Staging Score and the BALAD Score. *Oncology* 75: S83-S90.
71. Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, et al. (2009) Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology* 137: 110-118.
72. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, et al. (2006) Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol* 44: 723-731.
73. Guglielmi A, Ruzzenente A, Pachera S, Valdegamberi A, Sandri M, et al. (2008) Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma in a cohort of patients who underwent radiofrequency ablation with complete response. *Am J Gastroenterol* 103: 597-604.
74. Kudo M (2007) Review of 4th Single Topic Conference on HCC. Hepatocellular carcinoma: International consensus and controversies. *Hepatology* 37 Suppl 2: S83-87.
75. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, et al. (1998) Early hepatocellular carcinoma as an entity with a high rate of surgical cure. *Hepatology* 28: 1241-1246.
76. Zhang B, Yang B (1999) Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. *J Med Screen* 6: 108-110.
77. Lencioni R, Piscaglia F, Bolondi L (2008) Contrast-enhanced ultrasound in the diagnosis of hepatocellular carcinoma. *J Hepatol* 48: 848-857.
78. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, et al. (1992) Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. *Hepatology* 16:132-137.
79. Makuuchi M, Kokudo N, Arai S, Futagawa S, Kaneko S, et al. (2008) Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatology* 38: 37-51.
80. Nouse K, Tanaka H, Uematsu S, Shiraga K, Okamoto R, et al. (2008) Cost-effectiveness of the surveillance program of hepatocellular carcinoma depends on the medical circumstances. *J Gastroenterol Hepatol* 23: 437-444.
81. Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, et al. (2004) Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology* 126: 1005-1014.

82. Zhang BH, Yang BH, Tang ZY (2004) Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 130: 417-422.
83. Trevisani F, De Notariis S, Rapaccini G, Farinati F, Benvegnù L, et al. (2002) Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). *Am J Gastroenterol* 97: 734-744.
84. Santagostino E, Colombo M, Rivi M, Rumi MG, Rocino A, et al. (2003) A 6-month versus a 12-month surveillance for hepatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus. *Blood* 102: 78-82.
85. Kim DY, Han KH, Ahn SH, Paik YH, Lee KS, et al. (2007) Semiannual surveillance for hepatocellular carcinoma improved patient survival compared to annual surveillance (Korean experience). *Hepatology* 46: 403A.
86. Andersson KL, Salomon JA, Goldie SJ, Chung RT (2008) Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 6: 1418-1424.
87. Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, et al. (2003) Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *J Med Screen* 10: 204-209.
88. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, et al. (2011) Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. *Hepatology* 54: 1987-1997.
89. Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, et al. (2007) Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technol Assess* 11: 1-206.
90. Trevisani F, Cantarini MC, Labate AM, De Notariis S, Rapaccini G, et al. (2004) Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis: effects on cancer staging and patient survival. *Am J Gastroenterol* 99: 1470-1476.
91. Nakashima TKM (1987) Hepatocellular carcinoma.
92. Bruix J, Sherman M; American Association for the Study of Liver Diseases (2011) Management of hepatocellular carcinoma: an update. *Hepatology* 53: 1020-1022.
93. EASL-EORTIC clinical practice guidelines (2012) management of hepatocellular carcinoma. European Association For The Study Of The Liver; European Organisation. For Research And Treatment Of Cancer. *J Hepatol* 56: 908-943.

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