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...
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 hemachromatosis, α1-antitripsin 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 antiviral 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 wide spread 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 ± 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, Nouso 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 hemophilics 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 as 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. Vellid 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, Rodríguez 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 to 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. Okai H, Kurioka N, Kim K, Kanno T, Kuruki 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, Lim W, Severino R, Wong LM (2000) Improved survival with screening for hepatocellular carcinoma. Liver Transpl 6: 320-325.

16. Bolondi L, Soffia S, Siringo S, Galiani 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, Detkay 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, Ito 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. IHIT Study Group. Inhibition of hepatocarcinogenesis by interferon therapy. Ann Intern Med 131: 174-181.

22. Ganne-Carrié N, Chastang C, Chapel F, Munz C, Paterson 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, Grameni 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 hepatocellular carcinoma: results from the HALT-C Trial. J Hepatol 43: 434-441.

28. Sánchez-Tapias JM, Cost J, Mas A, Brugueras 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, Saiito N, Kasi M, Jtsukawa H, Yoshino I, et al. (1988) Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B 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. Martinez SM, Crespo G, Navasa M, Forns X (2011) Noninvasive assessment of liver fibrosis. Hepatology 53: 325-335.

33. Bosch FX, Ribes J, Díaz M, Clíeries R (2004) Primary liver cancer: worldwide incidence and trends. Gastroenterology 127: 55-516.

34. Yasui K, Hashimoto E, Komorizono Y, Koike K, Arii S, et al. (2011) Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin Gastroenterol Hepatol 9: 428-433.

35. Craxi A, Cammá C (2005) Prevention of hepatocellular carcinoma. Clin Liver Dis 9: 329-346, vii.

36. Bruno S, Strollofili T, Colombo M, Bollani S, Benvegnú 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, Tsio 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. Lamprertico P, Viganò M, Manenti E, lavender 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. Sangal 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 carcinoma 2 cm: results from two Western centers. Hepatology 57: 1426-1435.

44. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbadi 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. Hepatol Int 3: 544-550.

47. Di Tommaso L, Franchi G, Park YN, Fiamengo B, Destro A, et al. (2007) Diagnostic value of HPS70, glycican 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) Computer tomography—an increasing source of radiation exposure. N Engl J Med 357: 2277-2284.

50. Trevisani F, D’Intino PE, Morrelli-Labate AM, Mazzafera 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. (2006) Classification of microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Groupe d’Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol 31:133-141.

52. Villanueva A, Mendoza B, Forner A, Reig M, Llovet JM (2010) Hepatocellular carcinoma: novel molecular approaches for diagnosis, prognosis, and therapy. Annu Rev Med 61: 317-328.

53. 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.

54. 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.

55. 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.

56. 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 Japanese Integrated Staging Score, the conventional Japanese Integrated Staging Score and the BALAD Score. Oncology 75: S83-S90.

57. 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.

58. Cillo U, Vitale A, Grigoletto F, Farinati F, Brosele A, et al. (2006) Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 44: 723-731.

59. Guglielmi A, Ruzzenente A, Pacher S, Valdegamberi A, Sandri M, et al. (2008) Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma: a cohort of patients who underwent radiofrequency ablation with complete response. Am J Gastroenterol 103: 597-604.

60. Kudo M (2007) Review of 4th Single Topic Conference on HCC. Hepatocellular carcinoma: International consensus and controversies. Hepatol Res 37 Suppl 2: S83-87.

61. Takayama T, Makucchi 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.

62. 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.

63. Lencioni R, Piscaglia F, Bolondi L (2008) Contrast-enhanced ultrasound in the diagnosis of hepatocellular carcinoma. J Hepatol 48: 848-857.

64. Barbosa L, Benzi G, Galani S, Fusconi F, Zorini 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.

65. Makucchi 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. Hepatol Res 38: 37-51.

66. Nousu 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.

67. 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.
Citation: Qasim A (2013) Role of Surveillance in Hepatocellular Carcinoma. J Gastroint Dig Syst 3: 159. doi: 10.4172/2161-069X.1000159

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 Notarisi S, Rapaccini G, Farinati F, Benvegnü 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, Bourciel 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 Notarisi 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-EORTC 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.