Management of Hepatocellular Carcinoma: An Update

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Preamble

The recommendations provided in this document provide a data-supported approach to the diagnosis, staging and treatment of patients diagnosed with hepatocellular carcinoma (HCC). They are based on the following: (a) formal review and analysis of the recently-published world literature on the topic (Medline search through early 2010); (b) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1]; (c) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the American Gastroenterology Association Policy Statement on Guidelines[2]; (d) the experience of the authors. These recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the American Association for Study of Liver Disease (AASLD) requires a category to be assigned and reported with each recommendation (Table 1). These recommendations are fully endorsed by the American Association for the Study of Liver Diseases.

Introduction

The incidence of hepatocellular carcinoma is rising in many countries,[3-8], but in a few areas such as Japan and Singapore, the incidence of HCC seems to have stabilized or even fallen slightly.[9,10] Care of the patient with HCC involves physicians from different disciplines, including hepatologists, surgeons, liver transplant teams, oncologists, interventional radiologists, and to some extent radiation oncologists. In most settings, the role of the hepatologist or gastroenterologist

in these multi-specialty groups (usually organized as Tumor Boards) is not based on specific expertise in the application of a given intervention, but rather in assessing the degree of liver function impairment prior to, during and after therapy. This specific expertise is important since HCC usually appears in the setting of underlying liver disease. This results in a degree of complexity that is not present in other cancer types that seldom compromise vital organ function. All this suggests that patients with HCC should be managed in multidisciplinary settings, with all legitimate treatment options available. Under these circumstances, the hepatologist is to be a focal point around whom the process revolves. At all times, the hepatologist should assess liver function and suitability of various therapies. The hepatologist should also be responsible for management of the liver disease before, during, and after cancer therapy. He/she must ensure that only treatments of proven value are administered, rather than treatments that are technically feasible but which have not been shown to enhance survival.

Surveillance for Hepatocellular Carcinoma

Definitions of the terms used in this section are given in Table 2. Surveillance for HCC involves more than simply applying a screening test or tests. Surveillance should be offered in the setting of a program or a process in which screening tests and recall procedures have been standardized and in which quality control procedures are in place. The process of surveillance also involves deciding what level of risk of HCC is high enough to trigger surveillance, what screening tests to apply and how frequently (surveillance interval), and how abnormal results should be dealt with (diagnosis and/or recall).

Surveillance for HCC has become widely applied despite, until recently, the absence of evidence of benefit. There is now a single randomized controlled trial of surveillance versus no surveillance that has shown a survival benefit to a strategy of 6-monthly surveillance with alphafetoprotein (AFP) and ultrasound.[11] This study, which was performed in China, recruited 18,816 patients who had markers of current or prior hepatitis B infection. Adherence to surveillance was suboptimal (less than 60%) but in the subjects in the

Table 1. Levels of Evidence According to Study Design

Grade	Definition
II	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case control analytic studies
II-3	Multiple time series
	Dramatic uncontrolled experiments
III	Opinion of respected experts
	Descriptive epidemiology

surveillance arm the HCC related mortality was reduced by 37%. Because of poor compliance these results probably represent the minimum benefit that can be expected from surveillance. Ideally, these results should be validated in other geographical areas and therefore, additional randomized controlled trials (RCT) assessing the benefits of surveillance are still considered necessary. However, in the West it is unlikely that such trials will ever be conducted.

The objective of HCC surveillance must be to decrease mortality from the disease. Fewer people should die from HCC, or if this is not possible, surveillance should at a minimum provide a meaningful improvement in survival duration. Other endpoints, such as stage migration (detecting earlier stage disease) and 5-year mortality rates are not appropriate surrogate endpoints. This has clearly been shown by analysis of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI), which demonstrated that these endpoints did not correlate with a reduction in disease-specific mortality.[12]

There are several sources of bias to be considered in assessing reports of surveillance studies, such as lead-time bias and length bias. Only an RCT can eliminate these biases completely. Several studies have shown that surveillance does indeed detect earlier disease (stage migration).[13-16] Uncontrolled studies, all subject to lead-time bias, have also suggested that survival is improved after surveillance.[13,14] Surveillance for HCC is widely practiced and can generally be recommended for certain at-risk groups. HCC detected after the

onset of symptoms has a dismal prognosis (0%-10% 5-year survival).[17] In contrast, small HCC's such as those that can be detected by surveillance can be cured with an appreciable frequency.[17-21] Five-year disease-free survival exceeding 50% has been reported for both resection and liver transplantation.[17,22-30] Patients surviving free of disease for this duration should be considered cured. For these patients it is highly likely that surveillance did indeed decrease mortality. In addition, since major advances in our ability to treat HCC are less likely to come from treating late stage disease, it is therefore important to find early stage disease.

Definition of the At-Risk Population

The decision to enter a patient into a surveillance program is determined by the level of risk for HCC. This, in turn, is related to the incidence of HCC, and it is incidence that most people use to assess risk. However, there are no experimental data to indicate what level of risk or what incidence of HCC should trigger surveillance. Instead, decision analysis has been used to provide some guidelines as to the incidence of HCC at which surveillance may become effective. An intervention is considered effective if it provides an increase in longevity of about 100 days, *i.e.*, about 3 months.[31] Although the levels were set years ago, and may not be appropriate today, interventions that can be achieved at a cost of less than about $50,000/year of life gained are considered cost-effective.[32] There are now several published decision analysis/cost-effectiveness models for HCC surveillance. The models differ in the nature of the theoretical population being analyzed, and in the intervention being applied. Nonetheless, these models have several results in common. They all find that surveillance is cost-effective, although in some cases only marginally so, and most find that the efficacy of surveillance is highly dependent on the incidence of HCC. For example, Sarasin et al.[33] studied a theoretical cohort of patients with

Table 2. Definitions

● Screening—application of diagnostic tests in patients at risk for HCC, but in whom there is no a priori reason to suspect that HCC is present.

● Surveillance—the repeated application of screening tests.

● Enhanced follow-up—the series of investigations required to confirm of refute a diagnosis of HCC in patients in whom a surveillance test result is abnormal. In addition to the use of additional diagnostic tests the interval between assessments is shorter than for surveillance since there is a concern that a cancer already exists.

● Lead-time bias—This is 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. Unless properly controlled, studies of surveillance will show enhanced survival simply because the cancer is diagnosed at an earlier stage.

● Length bias—This is the apparent improvement in survival that occurs because surveillance preferentially detects slow growing cancers. More rapidly growing cancers may grow too large to be treated between screening visits

Table 3. Groups for whom HCC surveillance in recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

Population group	Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)	Incidence of HCC
Surveillance recommended		
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis 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		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

Child–Pugh A cirrhosis and found that if the incidence of HCC was 1.5%/year surveillance resulted in an increase in longevity of about 3 months. However, if the incidence of HCC was 6% the increase in survival was about 9 months. This study did not include transplantation as a treatment option. Arguedas et al.,[34] using a similar analysis which did include liver transplantation in a population of hepatitis C patients with cirrhosis and normal liver function, found that surveillance with either CT scanning alone or CT scanning plus ultrasound became cost-effective when the incidence of HCC was more than 1.4%. However, this study has to be interpreted cautiously, because the performance characteristics of CT scanning were derived from diagnostic studies, not surveillance studies (see Surveillance Tests). Lin et al.[35] found that surveillance with AFP and ultrasound was cost-effective regardless of HCC incidence. Thus, for patients with cirrhosis of varying etiologies, surveillance should be offered when the risk of HCC is 1.5%/year or greater.

Another more recent analysis[36] concluded that surveillance with AFP alone was the most cost-effective strategy, although a combination of AFP plus ultrasound was the most effective strategy. The authors interpreted the literature to indicate that AFP was a more sensitive surveillance test for HCC than ultrasound. Our review of the literature comes to the opposite conclusion, in that AFP (or other serological tests) are less sensitive than ultrasound as a screening test for HCC. Their model assumes that surveillance would identify HCC's at three different stages,: <2 cm, 2-5 cm, and >5 cm. The target of surveillance is identification of an HCC at its earliest possible stage when treatment has the highest possible likelihood of cure.

HCC surveillance should be able to identify a lesion smaller than 3 cm, and preferably smaller than 2 cm. Therefore, this cost-effectiveness analysis overemphasizes the effect of using AFP as a surveillance test because it includes larger HCC lesions where AFP is more likely to be elevated. Other data suggest that it is rare for the AFP to be elevated in lesions that are smaller than 2 cm in diameter.[37,38]

Table 3 describes the groups of patients in which these limits are exceeded. These groups of patients are also discussed in more detail below. The above cost-effectiveness analyses, which were restricted to cirrhotic populations, cannot be applied to hepatitis B carriers without cirrhosis. A cost-effectiveness analysis of surveillance for hepatitis B carriers using ultrasound and AFP levels suggested that surveillance became cost-effective once the incidence of HCC exceeds 0.2%/year (Collier J and Sherman M, unpublished observations). The subgroups of hepatitis B carriers in which the incidence of HCC exceeds 0.2%/year are given in Table 3. These groups are discussed in more detail below.

Hepatitis B

Beasley et al., in a prospective controlled study showed that the annual incidence of HCC in hepatitis B carriers was 0.5%.[39,40] The annual incidence increased with age, so that at age 70 the incidence was 1%. The incidence in patients with known cirrhosis was 2.5%/year. The relative risk of HCC was about 100, *i.e.*, hepatitis B carriers were 100 times more likely to develop HCC than uninfected persons. Sakuma et al.[41] found the incidence of HCC in male Japanese railway workers was 0.4%/year. Both these populations were male and Asian, with the hepatitis B

infection likely acquired at birth or in early childhood. Uncontrolled prospective cohort studies in North America have indicated that the incidence of HCC in HBV carriers varies widely.[42-44] Villeneuve et al.[42] found no tumors in a cohort infected with HBV and followed for 16 years. McMahon et al.[43] reported an incidence of HCC of 0.26%/year in a study of HBV-infected individuals in Alaska. Sherman et al.[44] described an incidence of 0.46%/year in their cohort. In Europe, the presence of HCC in hepatitis B carriers occurs mainly in patients with established cirrhosis.[45,46] Non-Asian chronic carriers who are anti-HBe-positive with long-term inactive viral replication and who do not have cirrhosis seem to have little risk of developing HCC.[47-50] Whether surveillance is worthwhile in this population is not clear. This is not true for Asian hepatitis B carriers without cirrhosis, who remain at risk for HCC regardless of replication status.[47,51-53] Similarly, the risk of HCC persists in long-term HBV carriers from Asia who lose HBsAg, and these patients should continue to undergo surveillance.[54] In Caucasian hepatitis B carriers who lose surface antigen, the risk of HCC seems to decline dramatically.[55,56] The annual incidence of HCC in male hepatitis B carriers from South East Asia only starts to exceed 0.2% at about age 40[40] irrespective of the presence of cirrhosis or disease activity. In contrast, the risk for HCC in Caucasians is related to inflammatory activity and the presence of cirrhosis. Therefore, Asian men should undergo surveillance from age 40 onwards. HCC will occur in younger patients, but the efficacy of providing surveillance to all carriers younger than age 40 is likely to be low. The incidence of HCC in women is lower than in men, although age-specific incidence rates are not commonly reported. Nonetheless, it seems appropriate to start surveillance at about age 50 in Asian women. All hepatitis B carriers with cirrhosis, regardless of age should be screened for HCC. In the presence of a history of a first degree relative with HCC, surveillance should start at a younger age,[42,57] although what that age should be is hard to define. Africans with hepatitis B seem to get HCC at a younger age.[58,59] Expert opinion suggests that surveillance in these populations should also start at a younger age. Whether this is true in Blacks born elsewhere is uncertain. In Caucasian hepatitis B carriers with no cirrhosis and inactive hepatitis, as determined by a long term normal ALT and low HBV DNA concentration,[46-48,60] the incidence of HCC is probably too low to make surveillance worthwhile. However, there are additional risk factors that have to be taken into account including older age, persistence of viral replication, co-infection with hepatitis C or HIV, or the presence of other liver diseases. Nevertheless, even in the absence of cirrhosis, adult Caucasian patients with active hepatitis B disease are likely at risk for HCC and should be screened.

Hepatitis B genotype is also a factor that affects cancer risk, probably as a consequence of differences in duration and severity of hepatic inflammation over time. Genotypes A and D (the European and Middle Eastern genotypes) have been compared[49] as have genotypes B and C (the Asian genotypes).[61,62] Genotype A has a generally more favorable outcome than genotype D, and genotype C has a higher risk of cancer than genotype B.

There have been two publications that attempted to fine tune the selection of patients with chronic hepatitis B for surveillance. In order to most accurately target those individuals at greatest risk of HCC for surveillance, several "risk scores" have been developed both for hepatitis B and C. Yuen et al.[61] have derived a score by multivariate analysis using a cohort of more than 800 subjects with chronic hepatitis B followed for a median duration of of 67 months. The predictive factors for HCC that they identified included male gender, increasing age, higher HBV DNA levels (log copies/ml), core promoter mutations and the presence of cirrhosis. These factors were combined to develop a 5 and 10-year score for the risk of developing HCC. The authors suggested that this score could be used to identify patients who might benefit from surveillance. A similar study has been published using data from the REVEAL study.[63,64] These studies will ultimately be more useful for identifying patients who do not need surveillance, rather than those who do. The negative predictive value of these scores is therefore crucial, and has not yet been reported. Both of these risk scores need validation, and are therefore not ready to be used in practice.

Hepatitis C
The risk of HCC in patients with chronic hepatitis C is highest among patients who have established cirrhosis,[65-67] where the incidence of HCC is between 2%-8% per year. It should be noted that these data come from clinic-based studies. There is a single prospective population-based study of the risk of HCC in patients with hepatitis C.[68] In this study of 12,008 men, the presence of anti-HCV-positivity conferred a 20-fold increased risk of HCC compared to anti-HCV negative subjects. The presence or absence of cirrhosis was not evaluated. Hepatitis C infected individuals who do not have cirrhosis have a much lower risk of

developing HCC.[69,70] Based on current knowledge, all patients with hepatitis C and cirrhosis should undergo surveillance. In the HALT C study,[70] the 5-year risk of non-cirrhotics developing HCC was 4.8%. Whether it is cost-effective for these subjects to undergo routine surveillance has not been determined, but on the basis of prior cost-effectiveness analyses they would fall below the 1.5%/yr incidence cut-off value.

There have been several attempts to develop non-invasive markers to predict the stage of fibrosis[71-73] and if properly validated, these could be used to determine when to initiate surveillance. Similarly, several other markers may predict a significant risk for developing HCC. One such marker may be the blood platelet count. It has been suggested that the incidence of HCC in cirrhosis from hepatitis C only increases substantially once the platelet count is less than 100×10^9/L[67,74,75] regardless of liver function. This finding needs to be validated in additional populations. Other investigators have attempted to develop predictive indices based on panels of commonly performed serological tests such as alpha 2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, gamma-glutamyltranspeptidase, and the AST/ALT ratio.[73-76] However, these indices have yet to be validated before entering general use and cannot be recommended at the present time.

There has also been an attempt to develop a risk score for developing HCC in patients with chronic hepatitis C.[70] The cohort was derived from the HALT-C study, which identified older age, African American race, lower platelet count, higher alkaline phosphatase, and esophageal varices as risk factors for HCC. This score also requires validation before its use inpractice can be recommended.

Patients with cirrhosis from hepatitis B or C who cleared virus spontaneously (hepatitis B) or with treatment (hepatitis B or C) are likely to have a reduced risk of developing HCC. This risk reduction has been quantitated for patients with hepatitis C.[77] The results were expressed as risk reduction per person year. However, it is likely that the reduction in risk is not immediate, and probably increases with time. Thus it likely becomes cost-ineffective to provide surveillance for these patients at some point in time. However, since that point cannot be determined with any certainty, these patients should continue to undergo surveillance for HCC.

Finally, ultrasound-based transient elastography has been used to assess the risk of HCC.[78] Although promising, this state of the art technology is not sufficiently advanced to allow for routine HCC risk assessment.[64]

Coinfection With HIV

Patients who are co-infected with HIV and either hepatitis B or hepatitis C may have more rapidly progressive liver disease,[79] and when they reach cirrhosis they are also at increased risk of HCC.[80] The MORTAVIC study indicated that HCC was responsible for 25% of all liver deaths in the post-HAART era.[81,82] HCC developing in co-infected patients has been said to be more aggressive than in mono-infected patients.[81,83,84] If true, this would make it unlikely that surveillance would be effective. Surveillance is most effective for slow-growing cancers (length bias). However, until data are available that show that surveillance is ineffective, these patients should continue to undergo surveillance. Thus, the criteria for entering co-infected patients into programs for HCC screening are the same as for mono-infected patients, *i.e.*, criteria based on the stage and grade of liver disease as described above.

Cirrhosis due to Causes Other Than Viral Hepatitis

The incidence of HCC in cirrhosis caused by diseases other than viral hepatitis is, with some exceptions, not accurately known. Most of the studies of the incidence of HCC in alcoholic cirrhosis date from before the identification of the hepatitis C virus. Given that hepatitis C is relatively frequent in alcoholics,[85,86] most of the reported HCC incidence rates in earlier studies are likely to be over-estimates. However, alcoholic cirrhosis is clearly a risk factor for HCC. In one study, alcoholic liver disease accounted for 32% of all HCC's.[87] In an Austrian cohort with HCC, alcoholic liver disease was the risk factor in 35% of subjects.[88] In the United States, the approximate hospitalization rate for HCC related to alcoholic cirrhosis is 8-9/100,000/year compared to about 7/100,000/year for hepatitis C.[89] This study did not determine the incidence of HCC in alcoholic liver disease, but it does confirm that alcoholic cirrhosis is a significant risk factor for HCC and probably sufficient to warrant surveillance for HCC. With the recognition of steatohepatitis as a cause of cirrhosis has come the suspicion that this too is a risk factor for HCC. No study to date has followed a sufficiently large group of such patients for long enough to describe an incidence rate for HCC. In one cohort study of patients with HCC,[90] diabetes mellitus was found in 20% of patients as the only risk factor for HCC. Whether or not these patients were cirrhotic was not noted. Non-alcoholic fatty liver disease (NAFLD) has been described in cohorts of patients with HCC.[91,92] Since

the incidence of HCC in cirrhosis due to NAFLD is unknown, it is not possible to assess whether surveillance might be effective or cost-effective. No recommendations can be made whether this group should be screened for HCC or not. This does not preclude the possibility that surveillance is beneficial in this group, and future data may change this recommendation. Patients with genetic hemochromatosis (GH) who have established cirrhosis have an increased risk of HCC.[93-95] The relative risk of HCC is about 20. The standardized incidence ratio for HCC in cirrhotic GH is 92.9 (95% confidence interval [CI] 25-237).[9] The incidence of HCC in cirrhosis due to GH is sufficiently high (about 3%-4%/year) that these patients should be included in surveillance programs. The incidence of HCC in stage 4 primary biliary cirrhosis is about the same as in cirrhosis due to hepatitis C.[96] For cirrhosis due to alpha 1-antitrypsin (AAT) deficiency,[97,98] there are insufficient data from cohort studies to accurately assess HCC incidence.

Recent data has suggested that the risk of HCC in autoimmune hepatitis with cirrhosis is high enough to warrant surveillance.[99] Cirrhosis was present in all patients prior to the development of HCC, and in these patients the incidence was about 1.1%/year. This does not quite make the cut-off of 1.5% at which HCC surveillance becomes cost-effective. Therefore, no recommendation can be made regarding surveillance in this group.

Treated Chronic Viral Hepatitis

Hepatitis B. There is as yet no convincing evidence that interferon treatment of chronic hepatitis B reduces the incidence of HCC. Studies in Europe suggested that interferon therapy for chronic hepatitis B improved survival and reduced the incidence of HCC.[99-101] A study from Taiwan also indicated that successful interferon therapy, *i.e.*, the development of anti-HBe, was associated with a reduced incidence of HCC.[100] However, in these studies the event rate was low, and the sample sizes were relatively small. In contrast, a non-randomized, but matched controlled study from Hong Kong that included a larger cohort followed for longer periods found that the incidence of HCC was not decreased in the treated group.[102] A single RCT suggests that lamivudine treatment of chronic hepatitis B carriers with cirrhosis does reduce the incidence of HCC.[103] However, when those who developed HCC within the first year and who must have had the HCC prior to the initiation of lamivudine therapy were excluded, the statistical superiority of lamivudine versus placebo disappeared. Thus, whether

the risk reduction is real and sufficient following successful HBV therapy that surveillance becomes unnecessary is not clear. If a patient is a candidate for surveillance before the institution of treatment, it seems prudent to continue to offer surveillance even after therapy-induced seroconversion or therapy-induced remission of inflammatory activity. Patients with cirrhosis from hepatitis B who clear virus spontaneously or with treatment likely have a reduced risk of developing HCC, but this has not been quantitated. Therefore these patients should continue to undergo surveillance.

Hepatitis C. There are a number of studies evaluating the effect of treatment of chronic hepatitis C on the incidence of HCC. A single RCT in Japan suggested that the incidence of HCC was reduced in both responders and non-responders to interferon.[104] These results could not be confirmed in a second RCT from France.[105] The results of these and other studies were summarized in a meta-analysis, which concluded that the benefit is mainly seen in those who were successfully treated, *i.e.*, had a sustained virological response, and even then, the effect was small.[106] A number of studies have compared the incidence of HCC in treated patients with that in historical controls.[15,65,107-114] These have suggested that there is a reduced incidence of HCC in treated patients. However, there are no data that demonstrate that treating or eradicating hepatitis C completely eliminates the risk for HCC. Thus, it seems that patients with hepatitis C and cirrhosis who have achieved viral clearance on therapy should, at least for now, continue to undergo surveillance. Note that patients with treated or spontaneously inactivated chronic hepatitis B or C may show regression of fibrosis sufficient to suggest reversal of cirrhosis. The risk of HCC in these patients probably does not decrease proportionately with the improvement in fibrosis. There are many theories about the pathogenesis of HCC in these patients, but one common factor seems to be that repeated rounds of necrosis and regeneration are necessary. The steps required to initiate the carcinogenic pathway probably occur many years before the disease becomes inactive, and so the threat of HCC remains even if fibrosis decreases. Regressed cirrhosis is not a reason to withhold surveillance. Patients who clear virus prior to developing cirrhosis have a very low likelihood of developing HCC and do not warrant surveillance.

Other Predictive Factors for HCC

In the at-risk population, there are additional factors associated with an increased risk of HCC. These

include an elevated AFP concentration,[115-117] presence of macroregenerative nodules,[118] small and large cell dysplasia on biopsy,[67,119,120] irregular regeneration (irregular margins to regenerative nodules),[121] and increased labeling index for proliferating cell nuclear antigen or silver staining of the nucloeolar organizing region.[122-126] Although such patients are at more immediate risk of developing HCC, they will likely already be in surveillance programs because of other recognized risk factors such as cirrhosis or chronic hepatitis B. The increased risk, however, does not require a change in surveillance protocol.

The recommendations as to who should undergo surveillance are broad, and are based largely on modeling studies which demonstrate specific cut-offs of HCC incidence at which surveillance became cost-effective.[33-36] However, within these groups there are individuals whose cancer risk is low, and for whom surveillance might not be necessary. For example, only about 15-25% of male Asians over age 40 with hepatitis B will ultimately develop HCC. The REVEAL study and other investigations[127,128] have clearly shown that in patients with hepatitis B, the risk of developing HCC increases with viral load even when this was measured years before the development of HCC. In assessing risk for patients with chronic hepatitis B infection, it is important to take these studies into account. However, it is also important to recognize the limitations of the studies. These findings apply to patients infected with genotype B and C, and may not be applicable to patients infected with other genotypes. Patients recruited into these studies were at least 30-35 years old, so the findings do not apply to younger patients. Finally, at least in the REVEAL study, even those in the lowest viral load stratum had an incidence of HCC of 0.73%/year which exceeds the 0.2%/year cut-off used to decide whether surveillance should or should not be undertaken in patients with chronic hepatitis B (see Table 3).[64]

Recommendation

1. Patients at high risk for developing HCC should be entered into surveillance programs (Level I). The at-risk groups for whom surveillance is recommended are identified in Table 3.

Surveillance of Patients on the Liver Transplant Waiting List

There are several reasons for screening patients on the liver transplant waiting list. Patients should be screened for HCC to identify small tumors that might require therapy, and to identify patients who develop cancer that exceeds the guidelines for transplantation. In addition, in the United States, under the current UNOS criteria the development of HCC provides liver transplant priority. Thus, it would seem to be in a patient's interest to have a small HCC diagnosed while on the liver transplant waiting list. One cost-efficacy analysis has suggested that the increase in longevity over the whole cohort of patients awaiting transplant is negligible, because although there may be an increase in longevity in those who develop HCC, it is countered by the loss of longevity in other patients on the waiting list whose transplants are delayed so that the patient with HCC can have priority.[129] In contrast, identification of HCC that exceeds guidelines, and resultant de-listing of such patients, is beneficial to other patients on the waiting list. Another analysis suggested that there were benefits to treating patients with HCC on the transplant waiting list with either resection or local ablation.[130] The benefit depended in part on the length of the waiting list. The longer the wait, the greater the benefit of intervention.

Recommendation

2. Patients on the transplant waiting list should be screened for HCC because in the USA the development of HCC gives increased priority for OLT, and because failure to screen for HCC means that patients may develop HCC that may progress beyond listing criteria without the physician being aware (level III).

Surveillance Tests

Any assay that is used to determine the presence or absence of a disease must be validated using a series of analyses that determine how well the test performs in diagnosing the disease (since no test is 100% accurate). The simplest measures are the sensitivity (true-positive rate) and specificity (true-negative rate), which are inversely related. For any single test and the underlying disease, as sensitivity increases, specificity decreases. Furthermore, the diagnostic accuracy of any test is related to the frequency of the underlying disease in the population being studied. This is measured by the positive and negative predictive values, *i.e.*, the rates at which positive or negative results are correct. An estimate of the efficiency of a test can also be obtained free of the influence of disease prevalence by using the Youden Index. This is a measure of the combined sensitivity and specificity (sensitivity/specificity-1). Finally since the performance characteristics of a test vary across the range of the test results the optimal cut-off for diagnosis can be obtained from the Receiver Operating Characteristics (ROC) curve, a plot of sensitivity vs. 1-specificity over the entire range of the test results. An important additional consideration is that the

natural history of sub-clinical liver cancer is not the same as for clinical cancer. In particular growth rates of sub-clinical cancer may be very different than tumor 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.

Screening tests fall into two categories, serological and radiological. Of the serological tests the performance characteristics of AFP have been best studied.[38, 131-133] 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.[38] 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%.[38] 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.[134] This was a prospective study evaluating 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 descarboxyprothrombin (DCP) were measured at

intervals, so that measurements were available at the time of diagnosis and 12 months prior to diagnosis. The results clearly show that both serological markers were inadequate for surveillance purposes, even when combined. Another recent study that suggested that AFP is a good surveillance test suffers from methodological flaws.[135] Among others, it was not really a surveillance study, but one in which the presence of HCC was known (i.e. a diagnostic study). Despite this fact, the performance characteristics of AFP were still inadequate, with a sensitivity of 66% and a specificity of 82%. Therefore, AFP is still considered an inadequate screening test for HCC.[38,136,137]

Another serological test used is the DCP, also known as Prothrombin Induced by Vitamin K Absence II (PIVKA II).[138-141] Most reports on the use of DCP have evaluated the use of this test 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 of this marker. There are also reports that DCP is a marker for portal vein invasion by tumor.[142] This would also suggest that DCP is not a good screening test. A screening test should be able to identify early disease, not late disease. The HALT-C study confirms that DCP is not a good surveillance tool.[134] Other tests that have been reported as screening tests included the ratio of glycosylated AFP (L3 fraction) to total AFP,[143-149] alpha fucosidase,[150,151] glypican 3[152,153] and HSP-70.[154-156] None of these has been adequately investigated and cannot be recommended as a screening test. Proteomic profiling may aid the development of more accurate markers.[156]

The radiological test most widely used for surveillance is ultrasonography. A small HCC on ultrasound may take on one of several different appearances. The smallest lesions may be echogenic, because of the presence of fat in the cells. Other lesions may be hypoechoic, or show a "target lesion" appearance. None of these appearances is specific. Ultrasound has been reported to have a sensitivity of between 65% and 80% and specificity greater than 90% when used as a screening test.[16] However, the performance characteristics have not been as well defined in nodular cirrhotic livers undergoing surveillance.[157-160)] These performance characteristics, although not ideal, are superior to any of the serological tests.

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.[155-157] 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.[161] No recommendation can be made about CT scanning for individuals in whom visibility on ultrasound is inadequate. It may be that some patients, particularly the obese, are just not good candidates for HCC surveillance despite their risk. Ideally, ultrasonographers performing HCC surveillance should receive special training, much as is done for mammographic surveillance in some jurisdictions.

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.[162] 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%.[162] Ultrasound alone cost about $2000 per tumor found, whereas the combination cost about $3000 per tumor found. [162]

Surveillance Interval

The ideal surveillance interval is not known. A surveillance interval of 6-12 months has been proposed based on tumor doubling times. The positive randomized control trial described earlier used a 6 month interval.[11] However, a retrospective study has reported that survival is no different in patients screened at 6 or 12 monthly intervals.[163] Another study 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.[164] 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. Only one (non-randomized) prospective cohort study has evaluated survival (in patients with hepatitis B) and demonstrated that survival is improved with 6 months surveillance intervals compared to 12 months.[165] Therefore, rather than making separate recommendations for patients with hepatitis B

or hepatitis C, we offer a single recommendation that surveillance be undertaken at 6 monthly intervals.

The decision to provide surveillance or not depends upon the magnitude of risk for HCC, but the surveillance interval is determined by the tumor growth rates and not by the degree of risk. This is an important concept because it means that the surveillance interval need not be shortened for patients who are thought to be at higher risk. However, 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 *a priori* 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.

Recommendations

3. Surveillance for HCC should be performed using ultrasonography (level II).

4. Patients should be screened at 6 month intervals (level II).

5. The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III).

Recall Policies

Recall policies are the policies instituted to deal with an abnormal screening test result. This is different than surveillance. The tests are different, and the interval of follow-up is different. Recall policies cover the investigations and follow-up that determine 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. The nodular cirrhotic liver poses problems in ultrasound interpretation. Early HCC can be difficult to distinguish from background nodularity. Some cirrhotic nodules can be as large as 2 cm. However, the majority of nodules smaller than 1 cm are not HCC.[166] It is also important to note that although classical HCC is described as hypoechoic on ultrasound, HCC can also be isoechoic with a halo, hyperechoic or of mixed echogenicity.

HCC

< 1 cm

> 1 cm

Repeat US at 3 months

4-phase MDCT/ dynamic contrast enhanced MRI

Arterial hypervascularity AND venous or delayed phase washout

Growing/changing character

Stable

Yes

Other contrast enhanced study (CT or MRI)

No

Investigate according to size

HCC

Arterial hypervascularity AND venous or delayed phase washout
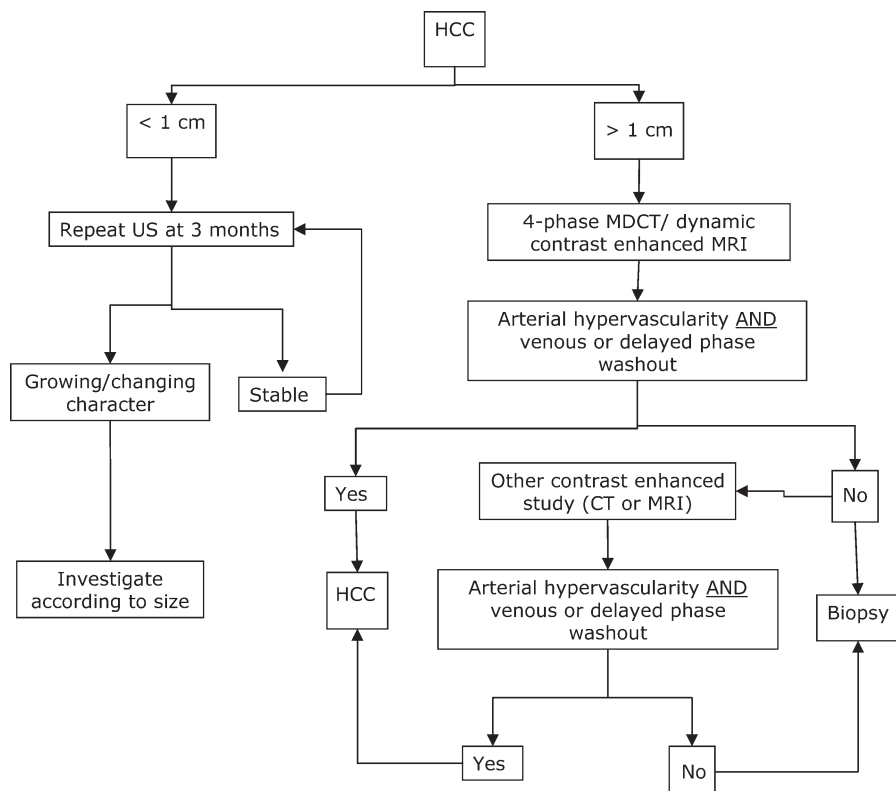
Biopsy

Yes

No

Fig. 1. Algorithm for investigation of small nodules found on screening in patients at risk for HCC (MDCT = multidetector CT scan).

Diagnosis of HCC

The tests used to diagnose HCC include radiology, biopsy and AFP serology. Which tests should be used depends on the context. Some form of imaging such as CT scan or MRI (most widely validated) is always required to determine the extent of disease.

Role of AFP in Diagnosis

Alphafetoprotein has long been used for the diagnosis of HCC. It has also been part of surveillance algorithms. However, as described above, the AFP is insufficiently sensitive or specific for use as a surveillance assay. Recent data also suggest that its use as a diagnostic test is less specific than was once thought. AFP can be elevated in intrahepatic cholangiocarcinoma (ICC). and in some metastases from colon cancer.[167,168] Therefore, the finding of a mass in the liver with an elevated AFP does not automatically indicate HCC. ICC is also more common in cirrhosis than in non-cirrhotics. Although the incidence of ICC is much lower than HCC, the fact that both are more common in cirrhosis means that care must be taken to distinguish between them given the differences in treatment and outcomes. Since AFP can be elevated in either condition, it is recommended that it no longer be used. Thus, the diagnosis of HCC must rest on radiological appearances and on histology.

Radiological Diagnosis of HCC

HCC can be diagnosed radiologically, without the need for biopsy if the typical imaging features are present.[72,74,169-174] This requires a contrast-enhanced study (dynamic CT-scan or MR). In the arterial phase, HCC enhances more intensely than the surrounding liver. This is because the arterial blood in the liver is diluted by venous blood that does not contain contrast, whereas the HCC contains only arterial blood. In the venous phase, the HCC enhances less than the surrounding liver. This is because HCC does not have a portal blood supply and the arterial blood flowing through the lesion no longer contains contrast, whereas the portal blood in the liver now contains contrast. This is known as "washout", although the term does not really describe the sequence of events. In the delayed phase, the presence of "washout" persists, and sometimes "washout" is only present in the delayed phase. The presence of arterial uptake followed by washout is highly specific for HCC.[172,173,175] Thus, to properly document the existence of HCC, a 4-phase study is required: unenhanced, arterial, venous and delayed phases.

In the previous guidelines,[176] we presented algorithms for the diagnosis of HCC that varied depending on the size of the lesion (Figure 1). Those algorithms were largely based on expert opinion, and relied on the typical appearances of HCC on contrast enhanced radiological studies as described above. The algorithm pertaining to lesions between 1-2 cm has now been partially validated. Forner et al.[175] used contrast ultrasound and MRI to evaluate lesions smaller than 2 cm found on surveillance. The positive predictive value of using these two tests was 100%, although the negative predictive value was only about 42%. This means that if both tests were positive the lesion was always HCC. However, if one or both tests were not conclusive, then the false-negative detection rate of HCC was greater than 50%. The algorithm requires that under these circumstances a biopsy be performed. In this study, up to three biopsies were performed in an attempt to come to the correct diagnosis. Contrast enhanced ultrasound is not available in the USA, so these results are not entirely applicable to a North American population. A second study came to very similar conclusions[177] providing external validation of the algorithm. A third study,[178] presented so far only in abstract form, used CT scanning as well as contrast ultrasound and MRI and has also validated the algorithm. These analyses showed that using a single contrast enhanced modality had a lower positive predictive value than using two studies, although the positive predictive value was still better than 90%. Other studies have provided external validation of these algorithms, but have also shown that typical appearances of arterial hypervascularity and venous washout are so highly specific that only a single study is necessary if these appearances are present.[178,179] The sensitivity of using dual imaging for diagnosis was between 21% and 37% and specificity was 100%. In addition, two studies have now shown that sequential imaging can be used to decrease the need for biopsy.[178,179] Using sequential studies rather than requiring two studies to be typical improved the sensitivity to about 74-80%, but the specificity fell to 89-97%. However, if atypical lesions were biopsied, the specificity was restored to 100%. Recent studies have also shown that intrahepatic cholangiocarcinoma (ICC) does not show washout in the venous delayed phases at MRI, further stressing the specificity of this profile at early stages.[180] At the same time, false positives for HCC have been described for contrast enhanced ultrasound in patients with biopsy proven ICC[181] if there is any discrepancy between imaging techniques, a biopsy should be obtained if treatment is to be considered. The algorithm for investigating lesions between 1-2 cm in diameter has been changed to reflect these considerations (Figure 1).

Although the recommendations for investigation of screen-detected lesions in the liver were developed for use in patients with cirrhosis, they apply equally well to patients with chronic hepatitis B who may not have fully developed cirrhosis. In both situations, the pretest probability of HCC being present is high. For nodules detected in an otherwise normal liver, the pretest probability of HCC is much lower and the guidelines do not apply.

Since radiological diagnosis is so crucial, it is essential that imaging be properly carried out. There are established protocols for the diagnosis of HCC that vary by the type of equipment used, define the amount of contrast to be given, the method of administering the agent, the timing of the studies after administration of contrast, and the thickness of the slices to be gathered. The physician ordering the tests should know whether the studies have been conducted under these defined conditions.

It should be noted that these algorithms are not infallible. There will be false-negative results on initial radiology studies, but these tumors should be detected on follow-up imaging before the lesion reaches a size where the likelihood of cure is decreased.

Much has been made of the entity of hypovascular HCC. This is a lesion that enhances less than the surrounding liver both on arterial and venous phase imaging. This is only a diagnostic problem for small lesions, (defined as <2 cm in diameter). Pathological study of these lesions has shown that the reason for the apparent hypovascularity is that they lesions have a dual blood supply.[182] They may have acquired some arterial supply, but this is not fully established. Histologically, unpaired arteries (no bile duct) are present but in small numbers, and there is still a portal blood supply although reduced. As the tumor matures, the blood supply becomes more arterialized and the lesion acquires the typical features of HCC. Dysplastic nodules also may show unpaired arteries and a reduced portal supply. Therefore, a biopsy is required to distinguish dysplastic nodules from HCC. Unfortunately, even with a needle biopsy, the hallmark features that distinguish a high-grade dysplastic nodule from HCC, namely stromal invasion, may not be detected. Larger HCC may also be hypovascular. These may also need biopsy, although the diagnosis will usually be evident without biopsy.

In addition to morphological features that help distinguish high-grade dyspastic nodules (HGDN) from HCC, there are several histological staining

characteristics which may be helpful. Markers of HCC vs. benign tissue include glypican 3,[183-185] heat shock protein (HSP) 70[155] and glutamine synthetase.[155] Staining for vascular endothelium with CD 34 is more usually positive and strongly positive in HCC as unpaired arteries more clearly identified, whereas in benign tissue the sinusoidal epithelium stains only weakly with this antibody. Cytokeratin stains for biliary epithelium (CK 7 and CK 19) should be negative, and a positive biliary cytokeratin stain makes HCC less likely.[186] Given the difficulty of making a positive diagnosis in tissue from small lesions, we recommend that pathologists use the full panel of stains listed above to help distinguish HGDN from HCC. Although occasionally other neoplastic lesions may stain positively with these markers, there should be little difficulty is distinguishing these from HCC on morphological grounds.

Thus, the current recommendations for the diagnosis of HCC are depicted in Figure 1. For lesions smaller than 1 cm, the recommendations remain unchanged. No detailed investigation is required, because most of these will be cirrhotic nodules rather than HCC. However, close follow-up at 3-month intervals is recommended using the technique that first documented the presence of the nodules. If these were detected by screening on ultrasound, then it is recommended that ultrasound should be the technique of follow-up.

For lesions above 1 cm in diameter, either dynamic MRI or multidetector CT scanner should be used. The technical specifications for best performance of these procedures have been previously described.[183] However, contrast enhanced ultrasound is less specific. If the appearances are typical for HCC on either MRI or CT scan, as described above, then no further investigation is required and the diagnosis of HCC is confirmed. If the appearances are not typical for HCC (and do not suggest hemangioma), then one of two strategies is possible. A second study (the other of CT scan or MRI) could be performed. If the appearances are typical, the diagnosis is confirmed. Alternatively, an atypical study could trigger a biopsy.

For this algorithm to be effective there must be strict adherence to imaging protocols[187,188] and strict application of the rules regarding vascularity and washout. The presence of arterial hypervascularity alone is insufficient, while the presence of venous washout is essential. Because performance of the study is so critical to the non-invasive diagnosis of HCC, it is recommended that these studies be performed in expert centers.

Pathological diagnosis of dysplasia and early HCC

The histological appearances of well-differentiated HCC and more advanced stages of HCC are well known and need no further discussion. However, one of the consequences of surveillance programs is the identification of smaller and smaller HCC's, as well as dysplastic nodules. The smaller the HCC lesion, the more difficult it is to distinguish malignant from benign nodules. This is true both radiologically and histologically.

Recently, a distinction has been made between "very early HCC"[189,190] and "small" or "progressed" HCC.[191,192] Early HCC, as defined by Japanese pathologists, is generally hypovascular,and has ill-defined margins.[169] Thus, it has a somewhat vague outline on ultrasound and may be hypovascular on CT scanning. Histologically, there are few unpaired arteries, but the cells show varying grades of dysplasia.[193] There may be invasion of the portal space by hepatocytes, but vessel invasion is absent. These lesions have been called "very early HCC" in the Barcelona Clinic Liver Cancer (BCLC) staging scheme.[194] The pathology of these "very early HCC" lesions has been defined in resected specimens, and therefore, the natural history of these lesions is unknown. However, the presence of small foci of typical HCC within them has been noted, suggesting that these lesions are precursors of typical HCC lesions.[189,191,192] The frequency with which these lesions develop typical HCC is unknown, In contrast, "small" or "progressed" HCC have well-defined margins on ultrasound, and exhibit the typical features of well-differentiated HCC on CT and on histology.[189,191,193] These lesions often show microvascular invasion, despite their small size.[193] The presence of microvascular invasion suggests that the prognosis of these lesions after treatment is less good than for "early HCC" where vascular invasion is rare. However, this has not been proven in clinical studies.

The classification and description of dysplastic nodules and early HCC has been recently revised to harmonize the approaches taken by Western and Japanese pathologists.[191] These studies have been undertaken on resected tissue, whereas samples from lesions detected on surveillance usually only have a needle biopsy to evaluate. It is important to recognize that rather than being individual discrete states, there is a continuum between HGDN and HCC. This complicates the evaluation of biopsies from small nodules.

Patients with liver nodules having a nonspecific vascular profile and negative biopsy should continue to undergo enhanced follow-up. There are no data to establish the best follow-up policy at this point, but repeated biopsy or follow-up CT/MRI to detect further growth should be considered. There are emerging data indicating that the smaller the lesion, the less

likely there is to be microscopic vascular invasion.[169] In addition, smaller lesions are more likely to be associated with treatment that will be curative.[190,195,196] Finally decision analysis also confirms that ideally, for the best outcome, the lesion should be smaller than 2 cm at diagnosis.[197] It is therefore important to make the diagnosis of HCC as early as possible. However, it is equally important not to apply invasive treatment to lesions that do not have any malignant potential and may still regress. This is a fine distinction that is not always possible to make. An additional concern about thin needle liver biopsy is the risk of bleeding and needle track seeding. Most studies that report needle track seeding do not specify the size of the lesion being biopsied.[198] Although the rate of needle track seeding after biopsy of small lesions (<2 cm) has not been accurately measured, it is probably uncommon. The current rate of bleeding from thin needle biopsy of small HCC has not been reported, but is probably no different than for biopsy of the liver in general.[198,199]

Recommendations

6. Nodules found on ultrasound surveillance that are smaller than 1 cm should be followed with ultrasound at intervals from 3-6 months (level III). If there has been no growth over a period of up to 2 years, one can revert to routine surveillance (level III).

7. Nodules larger than 1 cm found on ultrasound screening of a cirrhotic liver should be investigated further with either 4-phase multidetector CT scan or dynamic contrast enhanced MRI. If the appearances are typical of HCC (i.e., hypervascular in the arterial phase with washout in the portal venous or delayed phase), the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not typical, a second contrast enhanced study with the other imaging modality should be performed, or the lesion should be biopsied (level II).

8. Biopsies of small lesions should be evaluated by expert pathologists. Tissue that is not clearly HCC should be stained with all the available markers including CD34, CK7, glypican 3, HSP-70, and glutamine synthetase to improve diagnostic accuracy (level III).

9. If the biopsy is negative for patients with HCC, the lesion should be followed by imaging at 3-6 monthly intervals until the nodule either disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC a repeat biopsy is recommended (level III).

Staging Systems

The prognosis of solid tumors is generally related to tumor stage at presentation. Tumor stage also guides treatment decisions. However, in HCC patients the prediction of prognosis is more complex because the underlying liver function also affects prognosis. There is no worldwide consensus on the use of any given HCC staging system. However, most major trials of HCC therapy[199-203] have chosen the BCLC staging system,[17,194,200] making it the *de facto* reference staging system. "The BCLC can define patient groups for therapies across the continuum of disease extent seen with HCC. Hence, it has been widely and efficiently used in several major trials to define the patient population to be recruited and to stratify them into separate prognosis categories." In order to provide meaningful comparisons between the outcomes reported in these studies and the prognosis of individual patients. they have to be staged by the BCLC system (see below for details). This cannot at present be done with any other staging system. Therefore, all patients should be staged using the BCLC staging system. There are other staging systems in common use in the USA. These include the MELD score,[201,202] the TNM,[203,204] or simplified TNM staging system.[203,204] The MELD score was not designed to be an HCC staging system and does not provide good prognostic classification outside of patients who might receive a liver transplant because of liver failure. Although one study has suggested that the MELD score could replace the Child Pugh score in staging systems, this requires external validation.[201] MELD should not be used as general liver cancer staging system. The simplified TNM staging system as currently stated[203] requires evidence of microvascular invasion, something that is not available except in surgical specimens. The TNM system has been modified repeatedly[203-205] but still does not have adequate prognostic accuracy. In addition, its use is limited because it is based on pathological findings and liver function is not considered. A similar Japanese staging system suffers from the same drawbacks.[206]

The Okuda classification[207] takes tumor size (on imaging/surgery) and liver function into account. It allows the identification of end stage disease, but is unable to adequately stratify patients with early or intermediate stage disease. Elsewhere, several different staging systems have been developed, but none have achieved anything more than local acceptance and none except the BCLC link staging stratification with treatment choices.[208-212]
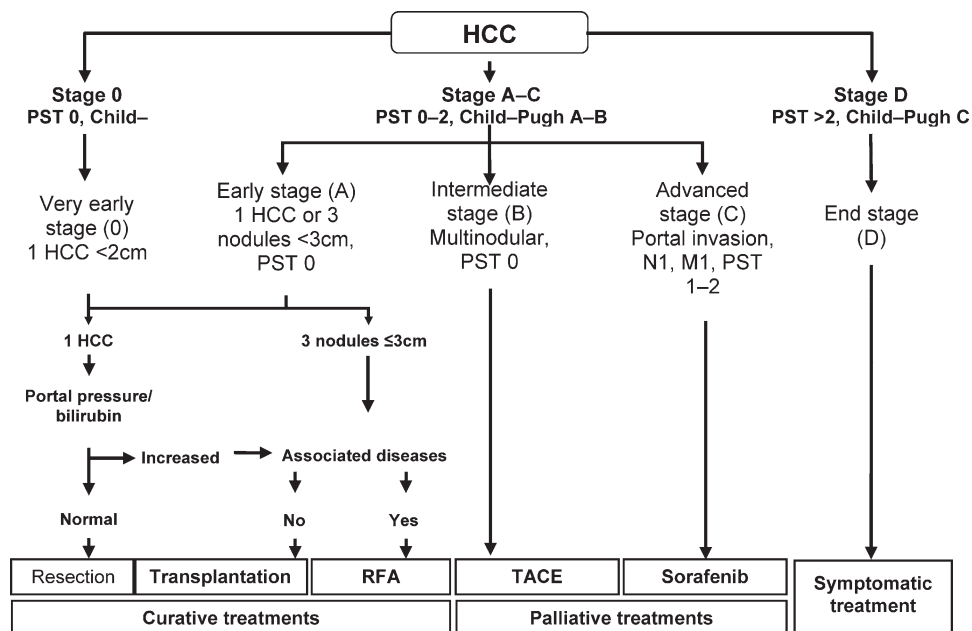
Fig. 2. The BCLC staging system and treatment allocation.

The BCLC staging system (Fig. 2)[17,194,200] was developed based on the combination of data from several independent studies representing different disease stages and/or treatment modalities and has been externally validated[37,213] It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms.[214-217] The main advantage of the BCLC staging system is that it links staging with treatment modalities and with an estimation of life expectancy that is based on published response rates to the various treatments. It identifies those with early HCC who may benefit from curative therapies, those at intermediate or advanced disease stage who may benefit from palliative treatments, as well as those at end-stage with a very poor life expectancy (Fig. 2). Early stage disease includes patients with preserved liver function (Child–Pugh A and B) with solitary HCC or up to 3 nodules ≤3 cm in size. These patients can be effectively treated by resection, liver transplantation or percutaneous ablation with possibility of long term cure, with 5-year survival figures ranging from 50% to 75%. Very early HCC is currently very difficult to diagnose confidently prior to treatment. In these lesions the absence of microvascular invasion and dissemination offers the highest likelihood of cure and thus, in Child–Pugh A patients may theoretically achieve a 5-year survival of almost 100%. The intermediate stage consists of Child–Pugh A and B patients with large/multifocal HCC who do not have cancer related symptoms and do not have macrovascular invasion or extrahepatic spread. Their survival at 3 years without therapy may reach 50%. These are

the optimal candidates for transarterial chemoembolization (TACE). Patients who present with cancer symptoms and/or with vascular invasion or extrahepatic spread comprise the advanced stage. They have a shorter life expectancy (50% survival at 1 year) and are candidates for sorafenib (see below). Finally, patients with extensive tumor involvement leading to severe deterioration of their physical capacity [WHO performance status >2][214] and/or major impairment of liver function (Child–Pugh C)[217] are considered end stage. Their median survival is less than 3 months.

Ongoing genomic and proteomic studies will characterize HCC more accurately, such that in the future HCC patients may be classified and treated according to their molecular profile and not according to the rough evaluation of tumor burden and conventional measures of liver function.

Recommendation

10. To best assess the prognosis of HCC patients it is recommended that the staging system take into account tumour stage, liver function and physical status. The impact of treatment should also be considered when estimating life expectancy. Currently, the BCLC system is the only staging system that accomplishes these aims (level II).

Treatment of Hepatocellular Carcinoma

Historically, the diagnosis of HCC was almost always made when the disease was advanced, when patients were symptomatic and presented with a variable degree of liver function impairment. At this late stage virtually no treatment had any chance of being

effective or of significantly improving survival. In addition, the morbidity associated with therapy (which was usually limited to surgical resection or systemic chemotherapy) was unacceptably high. Today, many patients are diagnosed at an early stage when liver function is preserved and there are no cancer related symptoms. In addition, there are several active treatments available that will potentially have a positive impact on survival.[194] However, to achieve the best outcomes requires the careful selection of candidates for each treatment option and the expert application of these treatments. Given the complexity of the disease and the large number of potentially useful therapies, patients diagnosed with liver cancer should be referred to multidisciplinary teams involving hepatologists, pathologists, radiologists, surgeons and oncologists. It is important to note that the level of evidence for most of the therapeutic options is limited to cohort investigations with few RCTs, most of which are limited to the treatment of advanced disease.[194,218] There are no large robust studies that compare treatments considered effective for early stage disease (surgical resection, transplantation, percutaneous ablation) nor are there studies comparing these methods to no treatment. Hence, any proposed treatment strategy has to be developed by analysis of several published cohorts of treated individuals. Availability of resources also has to be considered in developing treatment strategies. This is particularly relevant when considering liver transplantation, which is well established in the United States and Europe, but in some areas of the world transplantation is not available or is very limited. For patients with solitary HCC in the setting of decompensated cirrhosis and for those with early multifocal disease (up to 3 lesions, none larger than 3 cm)[219] the best option is liver transplantation,[17,194,220] but for patients with solitary tumors in well-compensated cirrhosis the optimal treatment strategy is still under debate.

It has become common to assess outcome through the use of the disease-free survival (DFS) rate. However, although this parameter is clinically informative, it can be misleading because it is a composite index registering two events: death and recurrence of tumor. This is especially relevant in HCC patients as they usually present with underlying cirrhosis and thus, they are at risk of death related either to cirrhosis itself or to tumor progression. Accordingly, different outcomes measured as DFS may be due either to differences in death rate, recurrence rate or both. Disease-free survival is commonly used as an endpoint in clinical trials of therapy in cancers other than the liver. However, given the potential contribution of the underlying liver disease and the potential effect that treatment-related hepatotoxicity might have on outcome, the use of this endpoint is discouraged.[220]

Thus, the preferred parameter for primary comparison between different therapies is survival. These comments are particularly relevant when discussing what the first treatment option should be in patients with cirrhosis and with early HCC, surgical resection or transplantation. In the following pages we will review the outcomes that might be achieved with the different therapeutic options that are currently available in conventional clinical practice. We will identify the selection criteria that should be used to offer each patient the option that provides the best long-term survival.

The therapies that are known to offer a high rate of complete responses and thus, a potential for cure, are surgical resection, transplantation and percutaneous ablation.[194,220] Among non-curative therapies transarterial chemoembolization and sorafenib have been shown to positively impact survival.[221,222] Other options such as arterial embolization without chemotherapy[223] or radioembolization do show some antitumor activity[224,225] but there is no proof of their benefit in terms of improved survival. Systemic chemotherapy with several agents has marginal activity with frequent toxicity, and is not associated with improved survival.[226,227] Finally, agents such as tamoxifen,[228] anti-androgens,[229,230] or octreotide[231,232] are completely ineffective.

Surgical Resection

This is the treatment of choice for HCC in non-cirrhotic patients, who account for just 5% of the cases in Western countries, and for about 40% in Asia. These patients will tolerate major resections with low morbidity, but in cirrhosis candidates for resection have to be carefully selected to diminish the risk of postoperative liver failure with increased risk of death. Right hepatectomy in cirrhotic patients has a higher risk of inducing decompensation than left hepatectomy. Two decades ago long-term survival was seldom achieved by resection. Today however, the 5-year survival after resection can exceed 50%.[27,28,190,233-235]

Several major advances have increased the long-term survival figures. Diagnosis during the asymptomatic phase of disease together with a more accurate staging of the patients has allowed the identification of patients with early stage disease. At the same time, more accurate evaluation of the underlying liver function has permitted the exclusion of those in whom the resection would likely prompt liver decompensation and death. For years the selection of candidates for

resection has been based on the Child–Pugh classification[217] but this is known to have inconsistent predictive value. Child–Pugh A patients may already have significant liver functional impairment with increased bilirubin, significant portal hypertension or even minor fluid retention requiring diuretic therapy.[217] These features indicate advanced liver disease[236-238] and preclude resection. Many Japanese groups rely on the Indocyanine Green retention test to assess whether surgery is feasible. The decision whether surgery is feasible and the extent of the resection that can be performed is made based on the degree of retention of the dye.[239] In contrast, in Europe and the United States, selection of optimal candidates for resection is usually based on the assessment of the presence of portal hypertension, as assessed clinically or by hepatic vein catheterization. Studies have shown that a normal bilirubin concentration, and the absence of clinically significant portal hypertension measured by hepatic vein catheterization (hepatic vein pressure gradient <10 mmHg) are the best predictors of excellent outcomes after surgery, with almost no risk for postoperative liver failure.[27,240] Such patients will not decompensate after resection and may achieve a 5-year survival of better than 70%.[27,201] In contrast, the majority of patients with significant portal hypertension will develop postoperative decompensation (mostly ascites), with a 5-year survival of less than 50%. Finally, the survival of those subjects with both adverse predictors (portal hypertension and elevated bilirubin) and/or multifocal disease is less than 30% at 5 years, regardless of their Child–Pugh stage.[27,235] Therefore, measurement of portal pressure is a key step in the evaluation of candidates for resection. Obviously, if upper endoscopy shows varices or if diuretic treatment is needed to control ascites, portal hypertension is already severe and catheterization is not necessary. Clinically significant portal hypertension may also be suspected when the platelet count is below 100,000/mm3 associated with significant splenomegaly. The usefulness portal pressure measurement to predict the outcome of patients and define optimal candidates for resection has been validated in Japan.[235] This study confirms that resection should remain the first option for patients who have the optimal profile, as defined by the BCLC staging system. Thus, although resection can be performed in some of these patients with advanced liver disease, the mortality is higher and these patients might be better served by liver transplantation or thermal ablation.

In recent years surgeons have refined both selection criteria and surgical techniques. Hence, blood transfusion may be needed in fewer than 10% of the cases and treatment related mortality should be less than 1%-3%.[27,171,241] The use of intra-operative ultrasonography allows precise localization and staging of the tumor, and also permits anatomical resections to be performed. From an oncological perspective anatomic resections that may include satellite lesions are more sound than limited resections without a surrounding margin. Pathological studies in resected tumors provide support for this notion[193] but some authors have challenged the benefits of a safety margin[242] and robust evidence is lacking.

Most groups restrict the indication for resection to patients with a single tumor in a suitable location for resection (as shown by dynamic CT scan, MRI, or other high resolution imaging techniques). The size of the tumor is not a clear-cut limiting factor. As discussed previously, the risk of vascular invasion and dissemination increases with size,[242] but some tumors may grow as a large single mass with no evidence of invasion. In these, surgery may be safely performed and the risk of recurrence is not significantly increased as compared to smaller tumors.[27,243]

Chemoembolization of the tumor prior to resection offers no benefit.[244] The same is true for the general use of portal vein embolization of the hepatic lobe hosting the tumor[245,246] to induce compensatory liver growth and functional capacity in the non-affected lobe prior to a major resection. It has also been suggested that malignant hepatocytes may also respond to the proliferative stimulus and this could result in uncontrolled tumor progression. In addition, portal vein obstruction may induce an acute increase in portal pressure and result in variceal bleeding. Clearly, large RCTs are needed to define the benefits and risks of these procedures.

Risk of Recurrence

After resection, tumor recurrence rate exceeds 70% at 5 years[27,243,247-250] including recurrence due to dissemination and *de novo* tumors.[251,252] The most powerful predictors of recurrence are the presence of microvascular invasion and/or additional tumor sites besides the primary lesion.[27,243,247-250,253] This suggests that the majority of recurrences are due to dissemination from the primary tumor and not metachronous tumors developing in a liver with cirrhosis.[251,254] Furthermore, recurrence due to dissemination is more likely to appear during the first 3 years of follow-up.[254] There is no effective adjuvant therapy that can reduce recurrence rates.[255] Preoperative chemoembolization or adjuvant chemotherapy are

not effective and may complicate the intervention. Internal radiation[256] and adoptive immunotherapy by activated lymphocytes[257] may have some anti-tumor efficacy but early promising results still have to be properly validated. This is also the case for retinoid administration[258] and interferon therapy.[259,260] Interferon alpha has been used to try to prevent post resection recurrence.[261] A recent meta-analysis of published studies[262] found that post-resection treatment with interferon did reduce the risk of HCC recurrence. However, it is not clear whether this outcome is independent of the effect of viral suppression or viral eradication. Therefore, interferon cannot yet be recommended as a general form of treatment following HCC resection.

As hoped in all cancers[263-265] molecular profiling of HCC is expected to refine risk assessment and several studies have been published trying to correlate abnormal gene expression with recurrence and outcome.[266-268] However, none of the proposed markers have gained wide acceptance or become routine in clinical practice.[269]

Treatment of recurrence is a poorly investigated area. Solitary recurrence might benefit from repeat resection, but in most patients recurrence after primary resection will be multifocal because of intra-hepatic dissemination from the primary tumor.[29,250,270] It has been suggested that patients with recurrence might be candidates for salvage transplantation.[271] Some retrospective analyses have suggested that the majority of patients with recurrence might benefit from this option.[29] However, this optimistic suggestion is not supported by an analysis of clinical outcomes. Most of the recurrences and specially those that appear early during follow-up are due to tumor dissemination and have a more aggressive biological pattern as compared to primary tumors.[250,251] Hence, only those patients in whom recurrence is due to *de novo* oncogenesis can be expected to benefit from salvage transplantation or repeated resection. Since the most accurate predictors of recurrence due to dissemination (vascular invasion, satellites) may be identified on pathology, and since the results of transplantation in these patients is good, some authors have proposed that this category of patients should be listed immediately after resection.[272] This might be more effective than waiting for recurrence to develop with excessive tumor burden possibly excluding liver transplantation. Organ allocation policies might have to be modified to take these findings into account.

Recommendations

11. Patients who have a single lesion can be offered surgical resection if they are non-cirrhotic or have cirrhosis but still have well preserved liver function, normal bilirubin and hepatic vein pressure gradient >10 mmHg (level II).

12. Pre or post-resection adjuvant therapy is not recommended (level II)

Liver Transplantation

Patients with HCC were frequently part of the initial experiences with liver transplantation because of the lack of alternative treatment and a dismal life expectancy. This was necessary to establish the feasibility of the intervention. At the same time, the initial results provided the rationale for the application of strict selection criteria to candidates who might benefit from the liver transplantation.[273,274] Patients with HCC that was detected only at surgery (incidental) because the lesion was too small to be detected by imaging techniques had an excellent outcome that did not differ from that of patients with non-malignant disease.[274] These tumors were those that were solitary and smaller than 5 cm. Later experience from France,[275] Italy,[219,276] Spain[276] and Germany[30] showed that excellent results could be achieved in patients with solitary HCC <5 cm or with up to 3 nodules smaller than 3 cm, these criteria being known as the Milano criteria after the seminal study by Mazzaferro et al.[219] The 5-year survival of these early stage patients exceeds 70%. This has confirmed early HCC as a clear indication for liver transplantation in conventional clinical practice.

The need to obtain the optimal benefit from the limited number of organs that are available has prompted the maintenance of strict selection criteria so as to list only those patients with early HCC who have the highest likelihood of survival after transplant. However, this means that some patients with a slightly more advanced HCC in whom transplant would offer an acceptable, but not excellent outcome, are excluded from the procedure.[25,277-279] This has recently fuelled a debate about whether and to what extent the indications for transplantation as therapy for HCC can be expanded.[25,280-285] There are very limited data to support extending the selection criteria.[188] The current more restrictive criteria were developed when imaging techniques were not as accurate as they are today and this has always meant a variable degree of under staging, ranging between 10% and 15%.[172,184,276] At the same time, in most programs the waiting time for transplant is long enough that there is a chance that the HCC will grow beyond the listing criteria. However, for patients with disease beyond standard listing criteria, if progression of disease has not been extensive

and there is no macroscopic vascular invasion or extra-hepatic spread, the survival is comparable to patients transplanted for disease within the standard listing criteria. Most groups describe a 5-year survival of around 50% in patients transplanted for extended criteria[25,277,286] and this is likely the lowest acceptable survival.[287,288] Thus, it is clear that there is some room to expand the criteria, but at present there are no data to define the new limits.

Most of the published studies that support an expansion of the limits are based on an analysis of explanted livers, information that is not available prior to surgery. There have been several strategies proposed to allow expansion of these criteria,[279,289,290] but methodological flaws mean that a robust assessment of novel criteria cannot be made. In most instances, the correlation with outcome is based on pathology reports; radiologic staging is not available or not uniformly performed. In some studies, the patients in the expanded population are analysed together with patients within the conventional Milan criteria, resulting in a dilution of the potentially poor outcome cohort with those individiuals having a good prognosis. Finally, registry data have shown that any expansion is associated with a reduction in life expectancy.[279,291] Hence, the critical decision is not to what extent listing criteria can be expanded, but by how much can the post-transplant life expectancy of the whole transplant cohort be lowered and still be acceptable, and what effect expanding the donor pool will have on mortality for non-HCC patients.[292] These are ethical issues that have not yet been resolved. At the same time, strong and validated imaging criteria for delisting upon minor progression potentially exceeding Milan definitions have not been defined.

The most powerful predictor of recurrence in the absence of extrahepatic spread is macro- or microscopic vascular invasion.[30,293] The likelihood of this event runs in parallel to tumor size and number.[193,294] Thus expanding the listing criteria is a very controversial issue, particularly when considering the shortage of donors. Tumor differentiation has been proposed to be a predictor for microscopic vascular invasion[283,295] but its assessment would require biopsy. Since large tumors are known to be heterogeneous, the accuracy of this strategy for clinical decision-making would be suboptimal. The lack of sufficient liver donation is the major limitation for liver transplantation. There is always a waiting period between listing and transplantation. This varies among programs but if long enough, the tumor will grow and develop major contraindications (vascular invasion, extrahepatic spread) to transplantation.[27,296] The rate of exclusion on the waiting list may be as high as 25% if the waiting list is longer than 12 months.[296,297] Obviously, if patients with more advanced tumors are included as a result of expanded listing criteria the dropout rate will be higher and this will translate into poor survival figures on an intention-to-treat analysis. Studies from Barcelona and San Francisco have shown that if the dropout rate due to advancing disease is 25% at 1 year this will translate into a 60% survival rate for transplantation based on an intention-to-treat analysis of patients listed for transplant (rather than those who actually undergo transplantation).[27,296] Data from Mount Sinai describe a 50% dropout rate with an even worse survival if the criteria for transplant are expanded.[298] Furthermore, one of the most important issues is the lack of clearly defined criteria for removing patients from the waiting list because of excessive tumor growth while waiting. If only major events (macroscopic vascular invasion and extrahepatic spread) are used to de-list patients this will mean that some patients will undergo transplantation who have too advanced disease. This will ultimately impair the survival figures for transplantation for HCC and put the whole program at risk. The listing of patients using expanded criteria will further worsen this scenario and thus, prior to any change in listing policy, it is essential to define the exclusion criteria.

Priority Listing for Transplantation

Following a federal request UNOS developed a priority system to transplant those with the highest short-term risk of mortality. The MELD score was selected as the most clinically useful tool for this aim as it accurately predicts early mortality in chronic liver disease of viral or alcoholic origin.[299] However, MELD is less powerful in predicting mortality in cholestatic liver disease and cannot predict mortality in HCC. To give patients with HCC equal opportunity for transplantation, HCC patients were initially given additional points aimed at matching the risk of death in end-stage cirrhosis: 24 points for solitary HCC < 2cm and 29 for solitary HCC 2 to 5cm or 3 nodules each <3 cm.[300] After implementation it was recognized that too high a priority was given to HCC patients and this was unfair to patients without cancer.[301] In addition, it was recognized that one fifth of the patients listed with an HCC diagnosis and who received priority, did not have HCC in the explanted liver. The points for HCC patients were therefore reduced to 20 and 29, to none and 24, respectively, and finally to none and 22, respectively.[300] In addition, a 10% point

increase is given for every three months on the waiting list. Results of the new points allocation are unknown. The MELD exception for HCC has resulted in an increased number of transplants being performed for HCC. In a recent consensus meeting,[188,302,303] new criteria for allocation points have been proposed and the future policy incorporates a 3 month waiting time to allow those fast progressing tumors to be detected and hence, not transplanted. Despite the exception, patients with HCC do not have as good a survival post transplant as compared to patients with equivalent MELD scores without HCC.[188,302,303]

The major difficulty in setting up fair and equitable priority policies is that there are no clear predictive data to identify patients at higher risk of progression and thus, of dropout. Patients with progression while waiting are clearly at higher risk, but some may have more aggressive tumors. Thus, if given excessive priority, the long-term results may be less than optimal because of HCC recurrence in the latter subset. Ongoing research should be able to clarify some of these key issues and in the future it should be possible to use clear clinical and molecular data to make clinical decisions regarding transplantation in patients with known HCC. In addition to the establishment of a priority policy, most groups treat the HCC upon listing, prior to transplantation. Unfortunately, this area also lacks robust RCTs comparing active intervention vs. no therapy or comparing several interventions to each other. All the evidence of benefit currently available comes from cohort assessments, usually using a per protocol rather than an intention-to-treat approach, or from Markov modeling using published clinical outcomes.

Despite some encouraging preliminary data,[304] later cohort studies suggest that systemic chemotherapy is ineffective.[305] Most groups perform transarterial chemoembolization upon listing because it reduces tumor burden and delays tumor progression.[306] However, it is known that in patients with decompensated disease this treatment may induce liver failure and death. Hence, it cannot be applied in all candidates. Patients with small tumors can have ablation either by percutaneous ethanol injection, radiofrequency or any other technique and statistical modeling has shown that such intervention is cost-effective if the expected waiting time is longer than 6 months.[130] The main concern with this approach is seeding due to tumor puncture as has been reported for diagnostic biopsy.[198] However, puncture-related seeding is usually restricted to poorly differentiated tumors and to peripheral tumors that cannot be approached through a rim of non-tumoral liver.[307,308]

Living Donor OLT

The most effective approach to reduce the dropout rate on the OLT waiting list is to expand the number of available livers. Several strategies (domino transplant using livers extracted from patients with amyloidosis, use of viral infected livers with minimal damage, split liver transplantation, non-beating heart donors) have been established for this purpose, but the best opportunity is the development of live donation.[309] After the first successful attempt[310] several thousand living donor operations have been performed worldwide using the right hepatic lobe. Results from Asia, US and Europe[311-316] that includes all the interventions performed suggest that the outcome after live donor transplantation is the same as with cadaveric donation. Interestingly, the value of the Milan criteria are further reinforced in this study since the survival and disease recurrence rates in patients transplanted with HCC are significantly different according to this stratification. In any case, long-term data are eagerly awaited. This is especially relevant for patients with hepatitis C virus infection in whom the potential severe recurrent liver disease is a matter of controversy.[317-320] Decision analysis taking into account the risk of dropout while waiting (4% per month), the expected survival of the recipient (70% at 5 years) and the risk for the donor (0.3-0.5% mortality) suggest that this is a cost-effective approach if the waiting time exceeds 7 months.[321] However, this is a complex intervention that should only be undertaken by expert surgeons to ensure the lowest morbidity and best outcome, not only to the recipient, but also to the donor. Complications may develop in 20% to 40% of the donors and the mortality risk for the donor is still 0.3% to 0.5%.[309] Finally, even with liver organ donation the number of donors is restricted because of blood group incompatibility, medical contraindications or psychosocial issues.

The development of living donation has further stimulated the discussion about expansion of the tumor burden limits for HCC patients. Since transplantation can be done with almost no delay and staging would be recent, several programs have proposed that living donation might be a valid option for those patients whose tumor stage does not allow listing for cadaveric liver transplantation. Cadaveric livers would then be allocated to patients with the best potential outcome (70% at 5 years), and living donation livers would benefit patients with a lower expectancy, around 50% at 5 years. There are no data to support utilizing such expanded criteria.[188]

Posttransplant Management

There are insufficient data to support or discourage any specific type of immunosuppression aimed at diminishing the growth of unrecognized tumor nests disseminated prior to the operation. Similarly, even if pathology discloses vascular invasion indicating a high risk for HCC recurrence there is no effective intervention to prevent or diminish this unfortunate event. The sole aspect that might be prevented by treatment is the viral re-infection of the graft. There are several effective strategies for hepatitis B[322] but in patients with hepatitis C the situation is less encouraging. The response rate in those patients who can receive combined therapy with pegylated interferon and ribavirin is reduced compared to the pre-transplant situation.[323] If viral replication persists, the new liver will develop infection that will cause significant liver damage leading to cirrhosis in enough patients and will affect both graft and patient survival.[317,324] Thus, the goal that transplantation may cure both the tumor and the underlying liver cannot be achieved, at least in the majority of HCC patients in Japan, the United States, and Europe, where hepatitis C is the major cause of HCC.

Recommendations

13. Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria: solitary tumor = 5 cm or up to three nodules =3 cm (level II). Living donor transplantation can be offered for HCC if the waiting time is expected to be so long that there is a high risk of tumor progression leading to exclusion from the waiting list (level II).

14. No recommendation can be made regarding expanding the listing criteria beyond the standard Milan Criteria (level III).

15. Preoperative therapy can be considered if the waiting list exceeds 6 months (level II).

Percutaneous Ablation

This is the best treatment option for patients with early stage HCC who are not suitable for resection or transplantation. In some Japanese centers this is offered as the first therapeutic option.[325] Destruction of tumor cells can be achieved by the injection of chemical substances (ethanol, acetic acid, or boiling saline) or by modifying the temperature (radiofrequency, microwave, laser, cryotherapy). Currently, radiofrequency ablation should be the the first choice for local ablation, but ethanol injection remains an important therapeutic tool. The efficacy of percutaneous ablation is assessed by dynamic CT 1 month after therapy.[326]

Although not entirely reliable, the absence of contrast uptake within the tumor reflects tumor necrosis, while the persistence of contrast uptake indicates treatment failure. The recurrence rate after ablation is as high as for resection. Some recurrences will occur in the vicinity of the treated nodule and are due to the presence of microscopic satellites not included in the ablation zone.

Percutaneous ablation is usually performed under ultrasound guidance. Ethanol injection is the best known and best studied approach.[327,328] Ethanol injection achieves necrosis rate of 90-100% of the HCC smaller than 2 cm, but the necrosis rate is reduced to 70% in tumors between 2 and 3 cm and to 50% in HCC between 3 and 5 cm.[329-331] Long term studies indicate that Child–Pugh A patients with successful tumor necrosis may achieve a 50% survival at 5 years.[28,195,327] This compares well with the outcome of resection in those candidates who do not fit the optimal surgical profile.[28]

Ethanol injection requires repeated injections on separate days and rarely accomplishes complete necrosis in tumors larger than 3 cm, because the injected ethanol cannot access the entire tumor volume. This may be due to the presence of intra-tumoral septa. To disrupt septae and facilitate ethanol infiltration, some authors have proposed that ethanol injection should be preceded by arterial embolization in large HCC.[332] The rate of initial response is enhanced but development of viable intra-tumoral nests or distant recurrence is the rule during follow-up and the long-term outcome is no different. Thus, there have been major efforts to develop alternative ablative techniques that would be able to necrose larger tumors in fewer treatment sessions.

Radiofrequency ablation (RFA) is the option that has better results in that regard. The insertion of single or multiple cooled tip electrodes or single electrodes with J-hooked needles that deliver heat around the tip induces a wide region of tumor necrosis. The efficacy of RFA in tumors <2 cm is similar to that of ethanol but requires fewer treatment sessions.[333,334] The efficacy in tumors >2 cm is better than with ethanol.[333-335]RCT have shown that RFA provides better local disease control that could result in an improved survival in RCT.[336,337] Large RCT comparing these two options in tumors >2 cm and primarily designed to assess survival are needed. The main drawback of radiofrequency is its higher cost and the higher rate (up to 10%) of adverse events (pleural effusion, peritoneal bleeding.[307,336,338]Procedure-related mortality ranges from 0% to 0.3%.[307,336,338] Subcapsular location and

poor tumor differentiation have been associated with increased risk of peritoneal seeding[307,308] and thus, this type of tumor should not be treated with RFA. Since the efficacy of radiofrequency is based on heat delivery and blood circulation inside the tumor may prevent proper heating, some authors have proposed combining radiofrequency with simultaneous vessel obstruction.[339] This maneuver may increase the area of necrosis,but the lack of evidence of a major benefit, together with the more complex process has prevented its wide implementation.

New studies have further confirmed the previous recommendations. A cumulative meta-analysis has suggested that survival is better after RFA than after ethanol injection.[335] As previously mentioned,data from a multicenter study in Italy that included patients with HCC lesions < 2 cm subject to RFA showed a 5-year survival of 70%, comparable to that of surgical resection in optimal candidates.[340] This provides the basis for a large randomised controlled trial comparing both options that is being developed in Japan. Hopefully, it will provide a definitive answer for the management of these patients.

A recent trial comparing the combination of chemoembolization and radiofrequency suggested that this approach offered an improvement in survival as compared to chemoembolization or ablation alone.[47] However, this article was retracted by the publishing journal.

A small randomized controlled trial comparing resection with radiofrequency ablation has been published.[341] Because of sample size limitations and the inclusion of a mixture of candidates with different stages of disease, the data suggesting equivalent outcomes with either option does not provide sufficient evidence to favor ablation as the first line option in patients who are also surgical candidates. Indeed, while resection ensures complete tumor removal in all tumor sizes, ablation has a significant proportion of failures in HCC lesions larger than 2-3 cm in size. Hence, the acceptance of ablation as a first-line treatment option is still controversial. The data reported by Livraghi et al.[340] in a cohort study with more than 200 patients meeting the optimal profile for resection should be confirmed by other groups before positioning ablation as the first line approach for very early HCC.

Recommendations

16. Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation (level II).

17. Alcohol injection and radiofrequency are equally effective for tumors <2 cm. However, the necrotic effect of radiofrequency ablation is more predictable in all tumor sizes and in addition, its efficacy is clearly superior to that of alcohol injection in larger tumors (level I).

Monitoring Response to Treatment

Efficacy of treatment is usually monitored radiologically. Effective treatment is indicated by lack of vascular enhancement in the treated lesion. Recurrence of tumour in the treated area or elsewhere is defined as re-appearance of vascular enhancement.[291] Thus, post-treatment monitoring must be performed with contrastenhanced imaging using CTor MRI. There are no data to indicate superiority of one modality over the other. In patients in whom the serum AFP level was elevated prior to treatment, and in whom AFP returned to normal after therapy, a subsequent rise in AFP may signalthe possibility of HCC recurrence. However, this is not reliable, and the monitoring of AFP levels after therapy does not replace imaging. The ideal imaging interval is unknown, but initially a 3-4 month interval is commonly used to monitor HCC lesions after initial treament. After about 2 years of recurrence-free survival, the interval of follow-up imaging examinations can be at less frequent intervals.

Non-Curative Treatment

As previously discussed, the end-point of therapy is to extend life expectancy. The only way to demonstrate this for any therapeutic option is to perform a properly powered RCT comparing active intervention vs. no treatment. The systematic review of the English literature during the last 25 years showed only a limited number of RCT that properly test the efficacy of palliative therapy[218] and the only options that have been proven to expand life expectancy in adequate trials are transarterial chemoembolization and sorafenib. Systemic chemotherapy with any of the available agents has marginal anti-tumor activity and no impact on survival.[227,232] Despite this lack of efficacy and the associated morbidity, chemotherapy (usually doxorubicin) is frequently administered in conventional clinical practice. Furthermore, it has also sometimes been used as a control arm in some research studies. This policy must be discouraged, since if a treatment is thought to be inactive and used as a placebo, it should at least be non-toxic and easy to administer. In fact, in the absence of effective therapy, the goal of health care providers should be to avoid unnecessary suffering with impairment of quality of life. Selective intra-arterial administration of any chemotherapy agent, frequently

suspended in lipiodol, has also negligible antitumor activity and robust data supporting survival benefit are lacking.[218,342] Selective radiation through intra-arterial injection of lipiodol-I-131[225,343] or Yttrium-90 labeled microspheres[224,344,345] has some antitumor activity but the impact on survival has not been established.

There are multiple other treatment modalities such as octreotide[342,343,346] interferon,[347] external radiation,[348] tamoxifen[228,349-356] or anti-androgenic therapy,[229,230,354] but none have been shown to improve survival. The first studies testing tamoxifen reported encouraging results[350,351] but unfortunately, larger, properly designed RCT, showed unequivocal negative results.[218,355,356] The absence of effect persists even when given at high doses[349] and thus we conclude that tamoxifen has no activity in patients with HCC. Some authors have suggested that HCC patients may have mutated estrogen receptors that cannot be blocked by tamoxifen[357] but by megestrol.[358] Again, the small number of patients in which this agent has been tested prevents any firm conclusion.

Transarterial Embolization and Chemoembolization

HCC exhibits intense neo-angiogenic activity during its progression.[166] At very early stages the tumor is not highly vascularised and its blood supply comes from the portal vein. As the tumor grows the blood supply becomes progressively arterialized, so that even well differentiated HCC is mostly dependent on the hepatic artery for blood supply. This characteristic provides the pathologic basis for the radiological characteristics that are used to diagnose the disease. It also provides the rationale to support arterial obstruction as an effective therapeutic option. Acute arterial obstruction induces ischemic tumor necrosis with a high rate of objective responses. Hepatic artery obstruction is performed during an angiographic procedure and is known as transarterial, or transcatheter arterial embolization (TAE). When TAE is combined with the prior injection into the hepatic artery of chemotherapeutic agents, usually mixed with lipiodol, the procedure is known as transarterial chemoembolization (TACE). Hepatic artery obstruction can be achieved by the injection or placement of several agents. Gelfoam carefully prepared as1 mm cubes is the most frequently used agent, but polyvinyl alcohol,[359] alcohol,[355] starch microspheres[360] metallic coils[361] or even autologous blood clots[362] have also been used. Gelfoam powder should be not be used as this may cause biliary damage.[363] The procedure requires the advancement of the catheter into the hepatic artery and then to lobar and segmental branches aiming to be as selective as possible so as to induce only minimal injury to the surrounding non-tumorous liver. Multifocal HCC involving both hepatic lobes may require the obstruction of the total hepatic artery blood flow.

Chemotherapy has to be injected prior to arterial obstruction. It is usual to suspend chemotherapy in lipiodol, an oily contrast agent used for lymphographic studies. Lipiodol is selectively retained within the tumor and this expands the exposure of the neoplastic cells to chemotherapy. The dose of chemotherapy to be administered has to be distributed among the affected lobes. If the tumor affects only one lobe, it is common policy to inject 25% of the agent into the lobe free of tumor with the objective of treating potentially undetected clones. Several chemotherapeutic agents have been used for TACE, but the most common is to inject adriamycin or cisplatin.[364]

TAE and TACE are considered for patients with nonsurgical HCC that are also ineligible for percutaneous ablation, provided there is no extrahepatic tumor spread. The main contraindication is the lack of portal blood flow (because of portal vein thrombosis, portosystemic anastomoses or hepatofugal flow). Patients with lobar or segmental portal vein thrombosis are poor candidates for TACE. First, TACE has not been adequately tested for safety or efficacy in these patients. Second, prognosis in patients with macroscopic vascular invasion is much worse that without portal vein invasion, so that data from patients without portal vein tumor thrombus cannot be extrapolated to those with tumor thrombus. TACE in these patients increases the risk of ischemic necrosis of viable liver and increase the risk of treatment-related death due to liver failure. Patients with advanced liver disease (Child–Pugh class B or C) and/or clinical symptoms of end-stage cancer should not be considered for these treatments as they have an increased risk of liver failure and death.

The side effects of intra-arterial injection of chemotherapy are the same as for systemic administration: nausea, vomiting, bone marrow depression, alopecia and potentially renal failure The development of polivinyl chloride spheres that release chemotherapy alter being injected have allowed a reduction of the side effects of the passage of chemotherapy into systemic circulation.[365-367] In addition, since the spheres are calibrated the arterial obstruction is predictable and the procedure is homogenised, while the antitumoral efficacy and safety are maintained, if not improved. Hepatic artery obstruction with acute ischemia of the HCC is associated with the so-called post-embolization

syndrome. This appears in more than 50% of the patients and consists of fever, abdominal pain and a moderate degree of ileus. Fasting is required for 24 hours and IV hydration is mandatory. Prophylactic antibiotics are not routinely used.[368] Fever is a reflection of tumor necrosis, but a minority of patients may develop severe infectious complications such as hepatic abscess or cholecystitis. The post-embolization syndrome is usually self-limited in less than 48 hours and the patients can be discharged from the hospital.

Both TAE and TACE induce extensive tumor necrosis in more than 50% of the patients.[218] Treatment response is assessed by the decrease in the concentration of tumor markers and the identification of large intra-tumoral necrotic areas and reduction in tumor burden in dynamic CT or MRI.[326] Immediately after arterial obstruction it is possible to see intra-tumoral bubbles that reflect tissue liquefaction. The evaluation of the treatment response should take into account the induction of intra-tumoral necrotic areas in estimating the decrease in tumor load, and not just a reduction in overall tumor size.[326] The fact that the Response Evaluation Criteria In Solid Tumours (RECIST) do not capture the extent of necrosis prompted the modification of the assessment of the therapeutic efficacy by registring the reduction of the viable tumor.[176,220,326] According to criteria that take into account the extent of necrosis. the reported rate of objective responses ranges between 16% and 60%[218,364] there being no differences between TAE and TACE. Fewer than 2% of treated patients achieve a complete response. During follow-up the residual tumor nests recover their blood supply and the tumor continues to grow. This consideration prompts treatment repetition either at regular intervals or "a la demande" as there is no prospective comparison to support one or other strategy.[364]

The tumor progression rate is reduced after treatment and this translates into a lower risk of vascular invasion. Response to treatment is associated with a significant improvement in survival. Cumulative meta-analysis of all published RCT's indicates that patient survival is significantly improved.[218] Until very recently, the gain in survival reported in individual trials was not statistically significant.[223,369-371] However, studies performed in Barcelona[372] and Hong Kong[373] reported a significant impact on survival have changed this negative statement. It has to be emphasized that the available trials are heterogeneous both in terms of patients profile, treatment schedule and agent used. Thus, it has still to be determined which are the best obstructing agents, the optimal chemotherapeutics and the most effective re-treatment schedule. The improve-

ment in survival in treated patients ranges from 20% to 60% at 2 years[364] but it is clear that the relevance of the improvement as compared to their outcome if untreated, is largely dependent on the patients baseline characteristics regarding tumor stage, liver function and general health status.

For patients who have either failed TACE, or who present with more advanced HCC new data indicates the efficacy of sorafenib in prolonging life. Sorafenib is a multikinase inhibitor with reported activity against Raf-1, B-Raf, VEGFR2, PDGFR, c-Kit receptors, among others receptor tyrosine kinases and serine threonine kinases.[374,375] A phase II trial involving 137 patients with advanced HCC showed that sorafenib induced partial responses in less than 5% of patients,[376] but the observed median survival of 9.2 months and median time to progression of 5.5 months provided the basis to develop a large randomized placebo controlled trial (SHARP).[221] This trial included 602 patients with advanced HCC, and was stopped at the interim analysis because of survival advantages favouring sorafenib (n = 299) vs. placebo (n = 303). Based on 321 deaths, the hazard ratio sorafenib/placebo was 0.69 (95% CI: 0.55, 0.86; P =0.0005), representing a 31% decrease in the risk of death with a median survival for sorafenib arm of 10.6 months vs. 7.9 months for placebo. In addition, sorafenib showed a significant benefit in terms of time to progression (TTP) with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo. The most frequent adverse events were diarrhea, fatigue, weight loss and hand-foot skin reaction. Grade 3/4 adverse events such as diarrhoea (sorafenib vs. placebo: 11% vs. 2%) and hand-foot skin reaction (8% vs. 1%) were more frequent with sorafenib. Drug discontinuation due to sorafenib adverse events occurred in 15%, but drug-related adverse events were considered manageable and no toxicity-related death occurred. The magnitude of the improvement of survival compares with other established molecular targeted therapies for advanced lung, colon, breast or pancreatic cancer.[175,377]

The efficacy of sorafenib in HCC has been reproduced in a randomized placebo controlled trial that included mostly patients with HBV-related HCC.[222] As a result, sorafenib is now established as first line treatment in patients with HCC who can no longer be treated with potentially more effective therapies. The SHARP trial included only patients with preserved liver (Child-Pugh A). Data in Child-Pugh B are scarce. The pharmacokinetic profile of sorafenib is similar in Child-Pugh A and B subjects. Cohort studies have suggested that the antitumour effect (tumour

progression) and safety profile are also similar. However, in the absence of robust evidence, the possibility for improved survival in Child-Pugh B patients should be carefully evaluated before initiating treatment. Clearly, patients who would be candidates for liver transplantation because of poor liver function and who have a poor short-term prognosis will not have a significant gain in life expectancy from sorafenib treatment.

Recommendations

18. TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (level I).

19. Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function (level I).

20. Tamoxifen, anti-androgens, octreotide or hepatic artery ligation/embolization are not recommended (level I).

21. Radioembolization with Yttrium90-labeled glass beads has been shown to induce extensive tumour necrosis with acceptable safety profile. However, there no studies demonstrating an impact on survival and hence, its value in the clinical setting has not been established and cannot be recommended as standard therapy for advanced HCC outside clinic al trials (level II).

22. Systemic or selective intra-arterial chemotherapy is not recommended and should not be used as standard of care (level II).

Treatment Algorithm

As previously stated, the establishment of an evidence based treatment strategy for HCC patients relies on fewer than one hundred RCT, assessing all of the possible treatment strategies. Almost all the treatment recommendations, therefore, are based on a critical reading of observational studies. In the clinical setting patients should be stratified by disease stage. For each stage there should be an indicated treatment. This is the basis for the BCLC scheme as depicted in Fig. 2.[17,19,194,200] The strategy combines in a single proposal staging, indicated treatment and estimation of prognosis, and it can be applied to the majority of patients evaluated for HCC.

Patients diagnosed at an early HCC stage are optimal candidates for resection, liver transplantation or percutaneous ablation. Resection is considered for patients with single tumors, absence of clinically rele-

vant portal hypertension and normal bilirubin. Tumor size is not a limiting factor, but it is uncommon to resect patients with tumors >5cm. Transplantation is considered in patients with 3 nodules <3 cm or with single tumors <5 cm with liver function impairment precluding resection. If a long waiting time (>6 months) is expected resection or percutaneous treatments are recommended prior to OLT. Living donor transplantation should also be considered. Percutaneous ablation is indicated in patients with small nonsurgical HCC. If these options are not feasible, patients have to be considered for palliation.

Transarterial chemoembolization is indicated in asymptomatic patients with multinodular tumors that have not invaded vessels nor been disseminated outside the liver. This type of patient is the best candidate for this approach, particularly if they still meet the criteria for Child–Pugh A stage. Treated patients who respond to therapy have an improved survival. Patients who present with a more advanced stage or who fail TACE are candidates for sorafenib provided they remain in Child-Pugh class A status with a good performance status. Patients with liver failure or physical impairment reflected by a markedly impaired performance status (>2)[214,215,378] will not benefit from any treatment option, even one with known efficacy in earlier disease. Finally, patients at a terminal stage with deeply impaired physical status (performance status >2) and/or massive tumor burden with heavily impaired liver function should receive symptomatic treatment to avoid unnecessary suffering.

Future Perspectives

This practice guideline has depicted the current status regarding the diagnosis, staging and treatment of HCC. As discussed, there are several areas where active research is needed, ranging from molecular pathogenesis to detection, diagnosis and treatment. The elucidation of the molecular steps that determine the transition from nonmalignant to malignant should allow the stratification of patients according to the distinct pathways that led to cancer and also provide for new preventive and therapeutic strategies. Identification of new biomarkers to establish the risk of cancer and/or detect its appearance at a preclinical stage is urgently needed. The current therapeutic approach also needs significant improvement. Treatments able to provide initial cure are hampered by a significant rate of disease recurrence and there is also a need for effective adjuvant therapies. Finally, the therapeutic options for patients with advanced HCC have limited impact and thus,

development of new agents and strategies for this group of patients is of major relevance. Fortunately, the awareness of these needs by official agencies such as the National Institutes of Health has increased the resources allocated for sponsoring research in this area. Hence, the action plan of the liver disease section (www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_ac-tion-_plan.htm) includes specific goals in the field of liver cancer. Hopefully, in the years to come the management of patients with HCC will offer a completely different perspective in which both prevention and treatment will have significantly decreased the number of HCC related deaths.

In the past decades HCC has gone from being an almost universal death sentence to a cancer that can be prevented, can be detected early, and can be cured with appreciable frequency given early detection. Since the incidence of HCC is increasing in most countries it is incumbent on physicians caring for patients at risk to be cognizant of the steps necessary to minimize the impact of this disease. This includes topics not covered in this guideline, such as vaccination against hepatitis B, effective treatment of chronic hepatitis B and C and other liver diseases, as well as topics that were discussed, such as providing high quality screening, proper management of screen detected lesions, and provision of therapy most appropriate for the stage of disease, that will provide the best long term survival.

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