Management of Hepatocellular Carcinoma

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Preamble

These recommendations 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 2005); (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 AGA Policy Statement on Guidelines[2]; (d) the experience of the authors in the specified topic. We have also reviewed the guidelines prepared at the time of the Monothematic Conference of the European Association for the Study of the Liver (EASL)[3]and the practice of authors experienced in the field. Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the 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

Over the last 5 to 8 years evidence has been accumulating in different countries that the incidence of hepatocellular carcinoma (HCC) is rising.[4-9] Traditionally, the care of patients with HCC has been undertaken by hepatobiliary surgeons, interventional radiologists, and oncologists. Hepatologists in North America are not trained to perform the procedures required to treat HCC, such as alcohol injection, radiofrequency ablation, or hepatic artery catheterization, although hepatologists in Japan and elsewhere may perform many of these procedures. As a result, the role of the hepatologist traditionally has been limited to making the diagnosis and providing care of the underlying liver disease. However, more recently, the role of the hepatologist has changed. First, in many centers the development of multidisciplinary clinics has emphasized the role of the hepatologist in assessing the patient's liver disease status, and carefully managing the liver disease before and during treatment. The hepatologist has also become more actively involved in deciding what form of therapy is most appropriate and whether the patient's liver function would allow that form of therapy to be given. In addition, arising out of caring for patients with end stage liver disease, hepatologists also institute surveillance for HCC and manage the investigation of abnormal results. Finally, hepatologists are involved in the decision whether or not to offer liver transplantation to patients with HCC.

There have been many reviews of various aspects of the care of patients with HCC, but only one clinical practice guideline has been published in the Western literature. The European Association for Study of the Liver (EASL) sponsored a single topic conference on HCC in 2000. The proceedings of this conference were published in 2001.[3] This document largely reflected practices in Europe, and possibly North America, whereas practices in Japan are somewhat different.

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 (surveil-

Abbreviaitons: CLT, Cadaveric liver transplantation; LDLT, live donor liver transplantation; PEI, Percutanoeus ethanol injection; RF, radiofrequency; TACE, Transarterial chemoembolization; PS, Performance Status.

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lance 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 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.[10] 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 surveillance arm the HCC related mortality was reduced by 37%. These results probably represent the minimum benefit that can be expected from surveillance, because of poor compliance. In contrast, an earlier study, also conducted in China failed to show benefit, largely because patients who were diagnosed with HCC did not undergo appropriate treatment.[11] 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. Such trials would be difficult to undertake, but are essential to unequivocally determine the benefit of surveillance in reducing HCC mortality. 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 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 a RCT can eliminate these biases completely. Several studies have shown that surveillance does detect earlier disease (stage migration).[13–16] However, as discussed above, this does not correlate well with reduction in disease-specific mortality. Uncontrolled studies, all subject to lead-time bias, have suggested that survival is improved after surveillance.[13,16]

Table 1. Levels of Evidence According to Study Design

Grade	Definition
I	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 authorities, descriptive epidemiology

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

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 HCCs 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 must be considered cured. For these patients it is highly likely that surveillance did indeed decrease mortality. 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-efficacy models for HCC surveillance. The models differ in the nature of the theoretical population being analyzed, and in the intervention being applied. Nonethe-

Table 3. Surveillance Is Recommended for the Follow Groups of Patients (Level III)

Hepatitis B carriers
Asian males ⩾ 40 years
Asian females ⩾ 50 years
All cirrhotic hepatitis B carriers
Family history of HCC
Africans over age 20
For non-cirrhotic hepatitis B carriers not listed above the risk of HCC varies depending on the severity of the underlying liver disease, and current and past hepatic inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammatory activity remain at risk for HCC.
Non-hepatitis B cirrhosis
Hepatitis C
Alcoholic cirrhosis
Genetic hemochromatosis
Primary biliary cirrhosis
Although the following groups have an increased risk of HCC no recommendations for or against surveillance can be made because a lack of data precludes an assessment of whether surveillance would be beneficial.
Alpha1-antitrypsin deficiency
Non-alcoholic steatohepatitis
Autoimmune hepatitis

less, 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 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. 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-efficacy analyses, which were restricted to cirrhotic populations, cannot be applied to hepatitis B carriers without cirrhosis. These patients, particularly in Asia and Africa, are also at risk for HCC. A cost-efficacy analysis of surveillance of hepatitis B carriers using ultrasound and AFP levels suggested that surveillance became cost-effective once the incidence of HCC exceeded 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%.[36-38] 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 the uninfected. Sakuma et al.[39] 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, where the epidemiology of hepatitis B is different, *i.e.*, hepatitis is acquired later in life, have indicated that the incidence of HCC in HBV carriers varies widely.[40-42] Villeneuve et al.[40] found no tumors in a cohort infected with HBV and followed for 16 years. McMahon et al.[41] reported an incidence of HCC of 0.26%/year in a study of HBV-infected individuals in Alaska. Sherman et al.[42] described an incidence of 0.46%/year in their cohort. In Europe HCC in hepatitis B carriers occurs mainly in patients with established cirrhosis.[43,44] 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.[45-48] 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.[45,49-51] Similarly, the risk of HCC persists in long-term HBV carriers from Asia who lose HBsAg, and these patients should continue to undergo surveillance.[52] In Caucasian hepatitis B carriers who lose surface antigen the risk of HCC seems to decline dramatically.[53,54]

The annual incidence of HCC in male hepatitis B carriers from South East Asia only starts to exceed 0.2% at about age 40[38]irrespective of presence of cirrhosis or disease activity. In contrast, in Caucasians the risk 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 hard to come by. 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 than 40,[55] although what that age should be is hard to define. Africans with hepatitis B seem to get HCC at a younger age.[56,57] 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 with inactive hepatitis, as determined by a long term normal ALT and low HBV DNA concentration[44,46,47,58] 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 and 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 disease are likely at risk for HCC, and should be screened.

Hepatitis C

The risk of HCC in patients with chronic hepatitis C is highest and has been best studied in patients who have established cirrhosis,[59-62] in whom 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.[63] In this study of 12,008 men being anti-HCV-positive 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.[64] However, the transition from bridging fibrosis to cirrhosis cannot be determined clinically so that the clinician cannot easily determine when these patients start to develop a significant increase in risk of HCC. For this reason the EASL conference[3] suggested that surveillance may be offered to patients with hepatitis C and cirrhosis or with bridging fibrosis or transition to cirrhosis. The cost-efficacy of this recommendation has not been evaluated. Based on current knowledge, all patients with hepatitis C and cirrhosis should undergo surveillance. Whether patients with bridging fibrosis should also undergo surveillance remains controversial.

There have been several attempts to develop non-invasive markers to predict the stage of fibrosis[65-67] and if properly validated, these could be used to determine when to initiate surveillance. Similarly, several other markers may predict a significant risk of HCC. One such marker may be the platelet count. It has been suggested that the incidence of HCC in hepatitis C cirrhosis only increases substantially once the platelet count is less than 100×10^9/L,[62,68,69] regardless of liver function. This needs to be validated. Others have attempted to develop predictive indices based on panels of commonly performed serological tests such as alpha 2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin and gamma-glutamyltranspeptidase and the AST/ALT ratio.[67,70] However, these indices have still to be validated before entering general use and cannot be recommended at present.

Co-infection With HIV

Patients who are co-infected with HIV and either hepatitis B or hepatitis C may have more rapidly progressive liver disease[71]and when they reach cirrhosis they are also at increased risk of HCC.[72] The MORTAVIC study indicated that HCC was responsible for 25% of all liver deaths in the post-HAART era.[73,74] 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[75-77] most of the reported HCC incidence rates in earlier studies must be over-estimates. That alcoholic cirrhosis is a risk factor for HCC is clear. In one study alcoholic liver disease accounted for 32% of all HCCs.[78] In an Austrian cohort with HCC alcoholic liver disease was the risk factor in 35% of subjects.[79] 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.[80] 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, 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[81] diabetes was found in 20% 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.[82,83] 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-efficient. 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.[84-86] 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.[87] For cirrhosis due to alpha 1-antitrypsin (AAT) deficiency,[88,89] or autoimmune hepatitis there are insufficient data from cohort studies to accurately assess HCC incidence.

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.[61,90,91] 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.[92] 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.[93] A single RCT suggests that lamivudine treatment of chronic hepatitis B carriers with cirrhosis does reduce the incidence of HCC,[94] but whether the risk reduction is sufficient 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.

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.[95] These results could not be confirmed in a second RCT from France.[96] The results of these 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.[97] A number of studies in Japan compared the incidence of HCC in treated patients with that in historical controls.[15,64,98-103] These have suggested that there is a reduced incidence of HCC in treated patients. However, no data 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 fibrosis is not a reason to withhold surveillance.

Other Predictive Factors for HCC

There are a number of factors associated with an increased risk of HCC that are seen in patients at risk for developing HCC. These include an elevated AFP concentration,[104-106] presence of macroregenerative nodules,[107] small and large cell dysplasia on biopsy,[62,108,109] irregular regeneration (irregular margins to regenerative nodules)[110] and increased labeling index for proliferating cell nuclear antigen or silver staining of the nucloeolar organizing region.[111-115] 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.

Recommendation

1. Patients at high risk for developing HCC should be entered into surveillance programs (Level I). The at-risk groups 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.[116] 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.[117] The benefit depended in part on the length of the waiting list. The longer the wait, the greater the benefit of intervention.

In the United States UNOS currently allows patients to be listed for liver transplantation with an elevated AFP without histological confirmation of HCC, even in the absence of a mass on imaging. It is important to note that AFP is being used here for diagnosis, not surveillance. Nonetheless, the performance characteristics of AFP, even as a diagnostic test are inadequate, particularly in the absence of a mass on imaging (see below).

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 and 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 incidence 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.[42,118-121] 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.[118] 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 HCCs 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 HCCs 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 vaule 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 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%.[118] 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 at birth the incidence of HCC is usually less than 1%.

Therefore, AFP is an inadequate screening test.[122] AFP still has a role in the diagnosis of HCC, since in cirrhotic patients with a mass in the liver an AFP greater than 200ng/mL has a very high positive predictive value for HCC.[118] Furthermore, a persistently elevated AFP has been clearly shown to be a risk factor for HCC.[104,105] Thus, the AFP can be used to help define patients at risk, but appears to have limited utility as a screening test.

Another serological test used to diagnose HCC is the des-gamma-carboxy prothrombin (DGCP), also known as Prothrombin Induced by Vitamin K Absence II (PIVKA II).[121,123-126] Most reports on the use of DGCP have evaluated the use of this test in a diagnostic mode, rather than for surveillance. Although there are reports of its use in a surveillance mode, these do not yet provide sufficient justification for routine use of this marker. There are also reports that DGCP is a marker for portal vein invasion by tumor.[127] If confirmed, this would also suggest that DGCP is not a good screening test. A screening test should be able to identify early disease, not late disease. Other tests that have been reported as screening tests included the ratio of glycosylated AFP (L3 fraction) to total AFP,[128-134] alpha fucosidase[135,136] and glypican 3.[137,138] 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.[139]

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 a 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[3,140-143] These performance characteristics, although not ideal, are superior to any of the serological tests. The major drawback to using ultrasound for HCC surveillance is that it is very operator dependent. In addition, scanning is difficult in obese subjects. Ideally, ultrasonographers performing HCC surveillance should receive special training, much as is done for mammographic surveillance in some jurisdictions.

Strategies such as alternating AFP and ultrasonography 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.[144] 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%.[144] Ultrasound alone cost about $2000 per tumor found, wheras the combination cost about $3000 per tumor found.[144] If ultrasonography is suboptimal or not available consideration can be given to using AFP surveillance. However, given the poor performance characteristics of AFP as a screening test consideration can also be given to not performing surveillance at all. Some reports suggest the use of CT scanning as a screening test for HCC.[143,145-147] This is problematic for several reasons. First, a screening test is not usually also the diagnostic test of choice. Second, the performance characteristics of CT scanning have been developed in diagnostic/staging studies and the performance characteristics of CT scanning in HCC surveillance are unknown. If CT scan is to be used as a screening test, *i.e.*, every 6-12 months over many years there is a significant radiation exposure to be considered. Practical experience suggests that the false-positive rate will be very high.

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.[10] However, a retrospective study has reported that survival is no different in patients screened at 6 or 12 monthly intervals.[148] Another study in HCV infected hemophiliacs without cirrhosis 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.[149] Thus, the surveillance interval remains controversial. Most experts use a 6-month interval, but there are no firm data to suggest that 6 months is better than 12 months. 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 surveil-

lance 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 not candidates for surveillance, but should be receiving enhanced follow-up.

Recall Policies

Recall policies are the policies instituted to deal with an abnormal screening test result. The first step is to define an abnormal result.[118] A mass which 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.[150] Therefore, in a cirrhotic liver any nodule larger than about 1 cm should be considered an abnormal screening result warranting further investigation. 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 ecogenicity.

Recommendations

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

4. AFP alone should not be used for sceening unless ultrasound is not available (level II).

5. Patients should be screened at 6 to12 month intervals (level II).

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

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 is always required to determine the extent of disease. In the setting of a patient with known hepatitis B or cirrhosis of other etiology a mass found incidentally or on screening ultrasound has a high likelihood of being HCC. The sequence of tests used to diagnose HCC depends on the size of the lesion

Lesions >2 cm in Diameter

Detection of a hepatic mass within a cirrhotic liver is highly suspicious of HCC. If AFP is greater than 200 ng/mL and the radiological appearance of the mass is suggestive of HCC (large and/or mutifocal disease with arterial hypervascularity), the likelihood that the lesion is HCC is high and biopsy is not essential.[151,152] If the imaging appearances are atypical, the differential diagnosis is broader, and tumor biospy should be considered.

The EASL conference[3] recommended that the diagnosis of HCC can be made without biopsy in patients with cirrhosis who have a mass >2 cm that shows characteristic arterial vascularization that is seen on two imaging modalities, *e.g.*, triphasic CT scan and MRI. Such lesions should be treated as HCC[3,151,152] since the positive predictive value of the clinical and radiological findings exceeds 95%.[3,151,152] If the vascular profile on dynamic imaging is not characteristic and the AFP is less than 200 ng/mL a biopsy is recommended. More recently the value of "washout" in the venous phase has been recognized. Thus, if the lesion shows arterial hypervascularity and washes out in the early or delayed venous phase, only a single imaging modality is required for diagnosis. This can be demonstrated on triphasic CT scan or MRI with gadolinium injection. However, such examinations should be conducted using state of the art equipment and read by radiologists with extensive expertise in liver radiology. Recent studies with contrast enhanced ultrasound indicate that this technique could also be used for this non-invasive diagnosis.[153-155] Other radiological tests that have been used to diagnose HCC are of less value for small HCC. In particular lipiodol angiography is not sensitive for small HCC.[156] Standard angiography and CT arterioportal angiography should not be routinely performed.

Lesions 1-2 cm in Diameter

Lesions between 1-2 cm in a cirrhotic liver found during surveillance have a high likelihood of being HCC. The EASL conference recommended that these lesions should be biopsied irrespective of their vascular profile.[3,3,151,152] If the vascular profile on dynamic imaging is not characteristic the diagnosis is less reliable and a biopsy should be performed.[151,152] It has to be stressed that biopsy of small lesions (<2 cm) may not be reliable. First, when the lesion is so small needle placement may be difficult and one cannot be certain that the sample did indeed come from the lesion. Second, there is disagreement between pathologists as to the dividing line between dysplasia and well-differentiated HCC,[157] and this disagreement occurs more frequently as the size of the lesion decreases. Finally, it may be difficult, if not impossible, to distinguish well-differentiated HCC from normal liver on biopsy, or from normal hepatocytes on fine needle biopsy, where the architectural features of HCC, such as widened

plates might be lost. One group has reported a high rate of diagnosis of HCC when small lesions found on ultrasound are biopsied.[158] However, in this study the reported pathologic features used for the diagnosis of HCC in minute nodules reflected advanced tumor stage not corresponding to early, well differentiated HCC, calling into question the validity of the findings. Recently, a distinction has been made between "very early HCC"[159,160] and "small HCC".[157,161] Early HCC, as defined by Japanese pathologists, is generally hypovascular, and has ill-defined margins. 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. There may be invasion of the portal space by hepatocytes, but vessel invasion is absent. These lesions are called "very early HCC" by Llovet et al.[17] 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.[157,161] The frequency with which these lesions develop typical HCC is unknown.

In contrast, "small HCC" have well-defined margins on ultrasound, and exhibit the typical features of HCC on CT and on histology.[157,161] These lesions often show microvascular invasion, despite their small size. 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 identification of features of early or "very early" HCC requires expert pathology interpretation, but if present should result in therapy being offered.[157] Therefore a positive biopsy is helpful, but a negative biopsy can never be taken as conclusive.

The characterization of a hepatic nodule <2 cm by imaging techniques is also more difficult. The vascular pattern on dynamic CT or MRI does not often show the specific pattern of arterial uptake followed by venous washout in the delayed portal/venous phase. Some minute nodules exhibit arterial enhancement without venous washout and these may correspond to lesions such as dysplatic nodules.[152,162-165] Up to 25% of small lesions <2cm with arterial enhancement, but without venous washout in cirrhotic livers will remain stable or regress over time and thus are not HCC.[151,162-166] Biopsy is therefore important in patients who do not exhibit typical radiological features.[151,162-166] While in nodules >2cm the imaging techniques offer sufficient confidence that diagnosis can be based on a single examination that shows the characteristic vascular profile (contrast-ultrasound, dynamic CT or MRI can be used for this purpose), in nodules between 1-2 cm the reliability of the recognition of the specific vascular pattern is not as good, so that it is advisable to use two dynamic imaging techniques to enhance the specificity of the findings. In practice, either CT or MRI must also be used for staging in all patients, since staging is critical to help determine the optimal treatment modality.

Patients with lesions 1-2 cm in diameter with a nonspecific vascular profile who have a 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.[161] In addition, the smaller the lesion the more likely it is that local ablation will be complete.[167] 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. 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.

Lesions Less Than 1 cm in Diameter

Finally, lesions <1 cm in diameter on ultrasound, particularly in a cirrhotic liver have a low likelihood of being HCC.[150] Malignancy is even less likely if they do not show contrast uptake on dynamic imaging.[168] Even if CT or MRI show tiny nodules with arterial vascularization, the vascularized areas may not correspond to HCC foci.[165,169] However, the possibility remains high that minute hepatic nodules detected by ultrasound may become malignant over time.[170,171] Therefore these nodules need to be followed-up every few months in order to detect growth suggestive of malignant transformation. Lack of growth over a period of more than 1-2 years suggests that the lesion is not HCC.

Figure 1 shows the suggested diagnostic strategy after detection of an hepatic nodule by ultrasound.

Recommendations

7. Nodules found on ultrasound surveillance that are smaller than 1 cm should be followed with ultra-

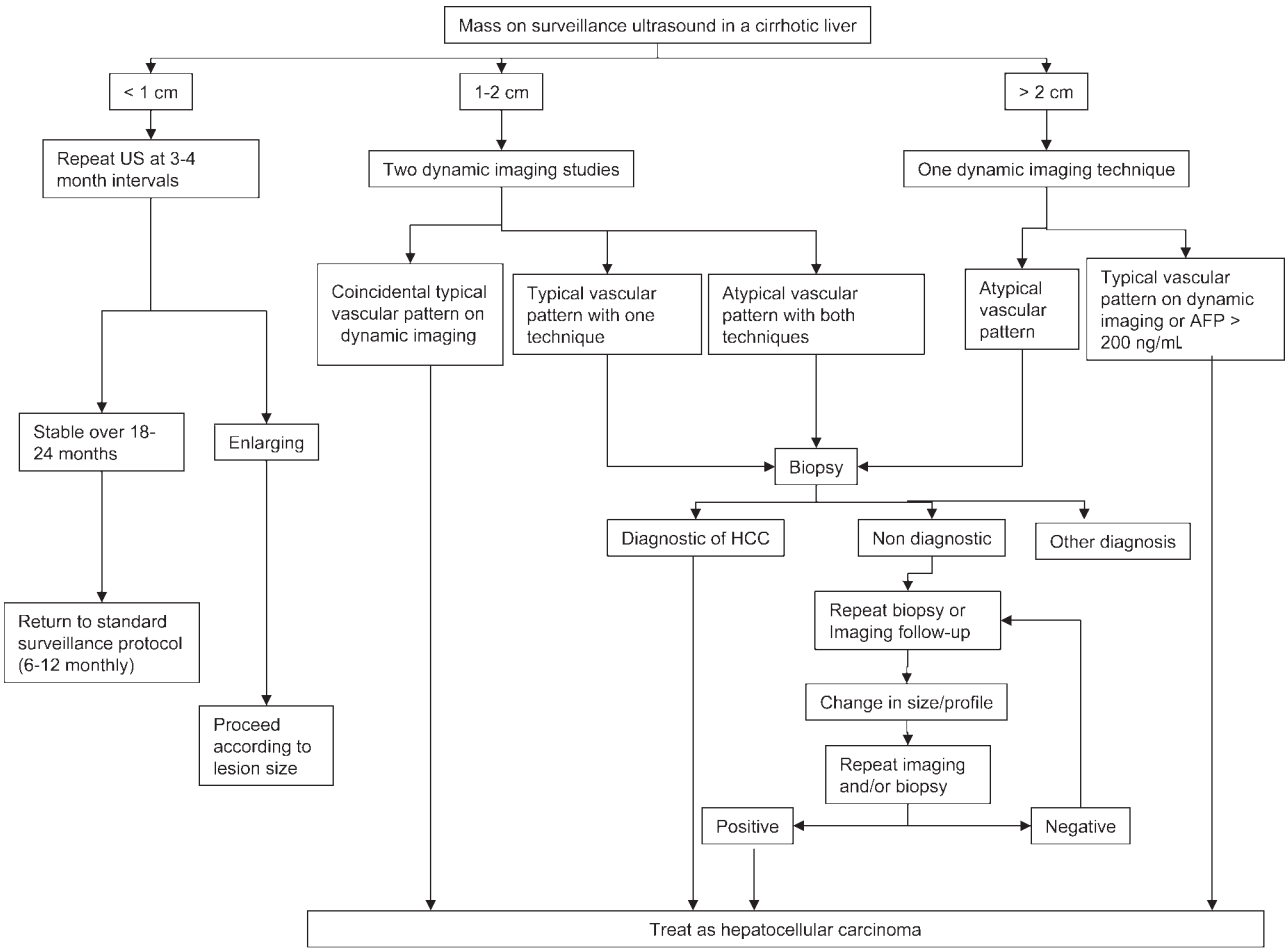

Fig. 1. A suggested algorithm for investigation of a nodule found on ultrasound during screening or surveillance. Note that nodules smaller than 1 cm initially which enlarge over time should be investigated using one of the other two algorithms shown depending on the size of the nodule. The typical vascular pattern referred to means that the lesion is hypervascular in the arterial phase, and washes out in the portal/venous phase. All other patterns are considered atypical.

sound 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).**

8. Nodules between 1-2 cm found on ultrasound screening of a cirrhotic liver should be investigated further with two dynamic studies, either CT scan, contrast ultrasound or MRI with contrast. If the appearances are typical of HCC (i.e., hypervascular with washout in the portal/venous phase) in two techniques the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not coincidental among techniques the lesion should be biopsied (level II).

9. If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC on a dynamic imaging technique, biopsy is not necessary for the diagnosis of HCC. Alternatively, if the AFP is > 200 ng/mL biopsy is also not required. However, if the vascular profile on imaging is not characteristic or if the nodule is detected in a non-cirrhotic liver, biopsy should be performed (level II).

10. Biopsies of small lesions should be evaluated by expert pathologists. If the biopsy is negative for HCC patients should be followed by ultrasound or CT scanning 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 and thus tumor stage 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 stag-

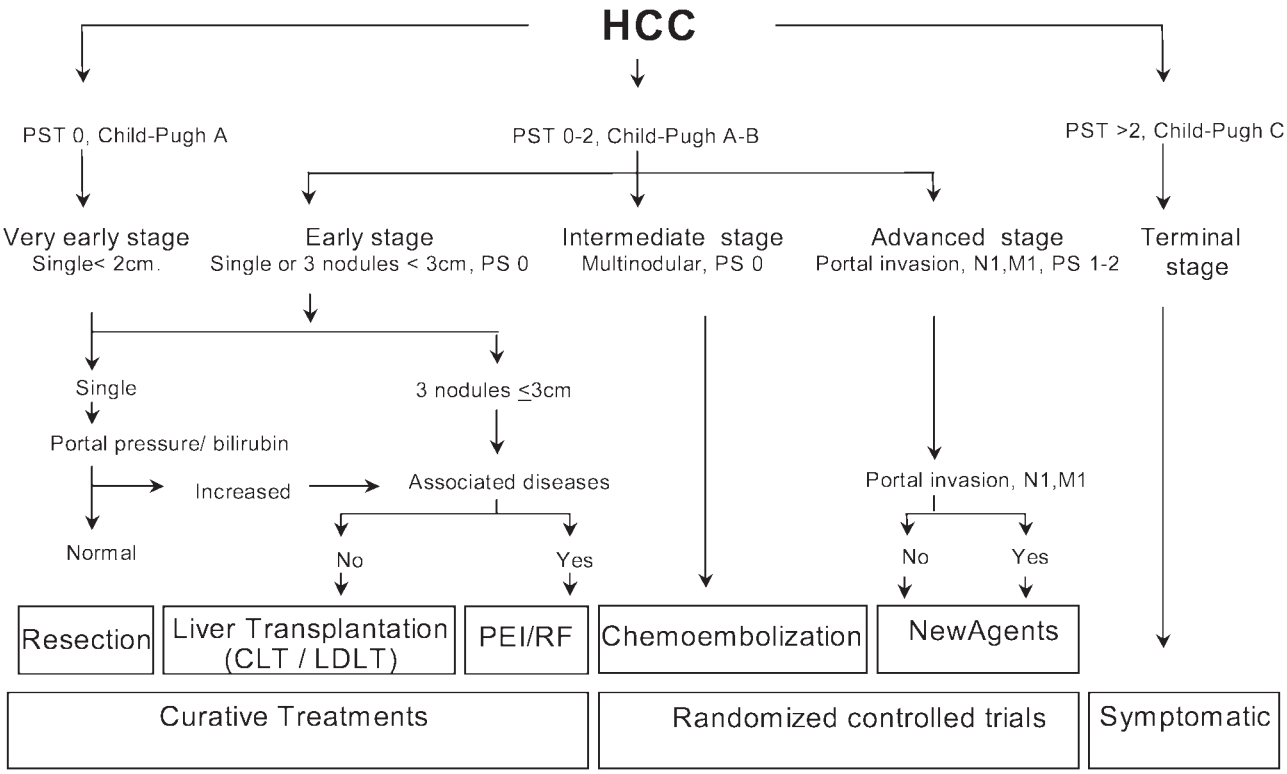

Fig. 2. Strategy for staging and treatment assignment in patients diagnosed with HCC according to the BCLC proposal.

ing system, and which is the preferred system remains controversial. Any staging system should classify patients into subgroups with significantly different outcomes, and at the same time should help to direct therapy. Historically, HCC has been classified by the TNM[172] or Okuda staging systems.[173] The TNM system has been modified repeatedly[174] and 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. An international multicentre study developed a score based on the evaluation of liver status (cirrhosis vs no cirrhosis) together with tumor staging according to the TNM classification,[175] but its validity has only been assesed in patients undergoing resection. The Okuda classification 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. The Child–Pugh system[176] and the MELD score[177,178] only consider liver function and thus, cannot be accurate. Several scoring systems have been developed in the last few years, attempting to stratify patients according to expected survival. Schemes have been proposed in Barcelona,[179] France,[180] Italy,[181] Austria,[182] China,[183] and Japan.[184,185] While these systems are able to divide patients into strata with different prognoses, these schemes are mostly helpful in identifying end-stage patients with a poor prognosis. Furthermore, most classification/staging systems do not take into account the effects of treatment, nor do they indicate optimal forms of treatment for different disease stages. Finally, when comparing results among systems none have been adequately cross-validated. The lack of reproducibility likely indicates heterogeneity among the different patient groups and this prevents the development of a universal staging system. Recently, Marrero et al.[186] and Grieco et al.[187] have compared all systems available and validated the BCLC system in U.S. and Italian patients, respectively.

The Barcelona-Clinic- Liver-Cancer (BCLC) staging system (Fig. 2)[19,188] was developed based on the combination of data from several independent studies representing different disease stages and/or treatment modalities. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms.[189-191] 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

Table 4. World Health Organization Performance Status grades

Stage 0	Fully active, normal life, no symptoms.
Stage 1	Minor symptoms, able to do light activity.
Stage 2	Capable of self-care but unable to carry out work activities. Up for more than 50% waking hours
Stage 3	Limited self care capacity. Confined to bed or chair > 50% waking hours.
Stage 4	Completely disabled. Confined to bed or chair.

(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 surgical ablation. 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. 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 to enter therapeutic trials with new agents. Finally, patients with extensive tumor involvement leading to severe deterioration of their physical capacity [WHO performance status >2] (Table 4)[191] and/or major impairment of liver function (Child–Pugh C),[173] 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

11. To best assess the prognosis of HCC patients it is recommended that the staging system takes into account tumor 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-2).

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.[17] 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 RCT, most of which are limited to the treatment of advanced disease.[192] There are no 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 from the 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 has very limited applicability. 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)[193] the best option is liver transplantation,[17] but for patients with solitary tumors in well-compensated cirrhosis the optimal treatment strategy is still under debate.[24]

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 (Fig. 3). 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 in DFS may be

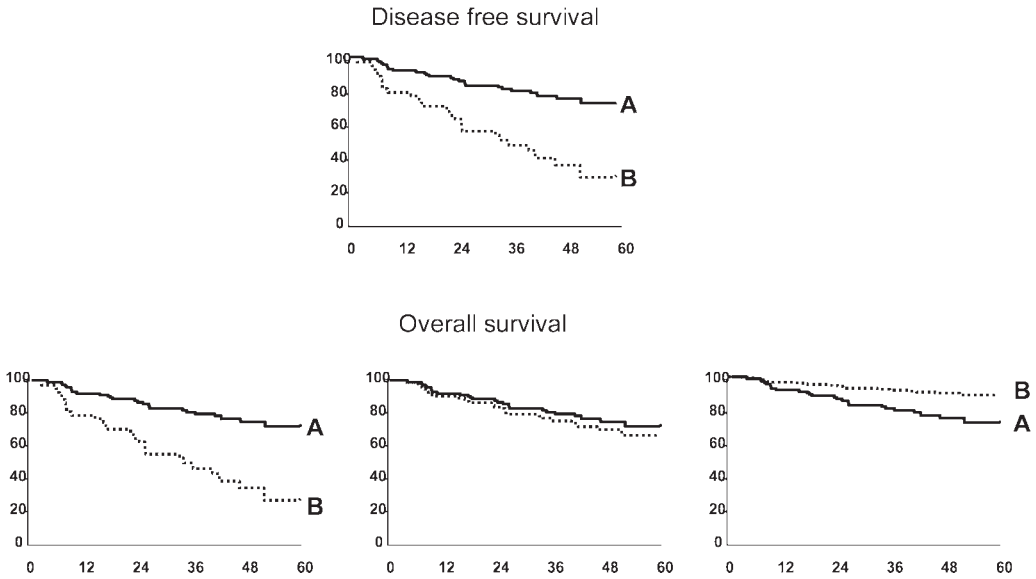

Fig. 3. Disease free survival (DFS)(upper panel) appears to be different between option A (continuous line) and option B (dotted line). However, the lower panel expresses outcome as overall survival and there are three different potential scenarios. Overall survival might truly be better for option A (left lower panel). Alternatively, the improved DFS for option A may be the result of a lower recurrence rate but similar death rate; overall survival would thus be similar to that of the control (central lower panel). Finally, the right lower panel depicts the worst possibility. In this scenario, option A is highly effective against HCC but is associated with treatment related deaths, while option B is safe but has minimal antitumoral efficacy. Thus, the overall survival is better with option B, and its lower DFS is due only to the lack of significant antitumoral effect with associated higher recurrence rates.

due either to differences in death rate, recurrence rate or both. Thus, theoretically, although a treatment might be less active against the tumor than another treatment and thus result in a higher recurrence rate after initial treatment, the overall survival might not differ or may even be better.

Thus, the preferred parameter for primary comparison between different therapies should be 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.[17] Among non-curative therapies the only one that has been shown to positively impact survival is transarterial chemoembolization.[192] Other options such as arterial embolization without chemotherapy[194] or internal radiation do show some antitumor activity,[195] 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.[196,197] Finally, agents such as tamoxifen,[192] anti-androgens,[198,199] or octreotide[200] 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%.[27,28,159,201,202]

Several major advances have increased of 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[176] 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.[176] These features indicate advanced liver disease[203,204] and preclude resection. Many Japanese groups rely on the Indocyanine Green retention test. 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.[205] 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 catheterisation (hepatic vein pressure gradient <10 mmHg) are the best predictors of excellent outcomes after surgery, with almost no risk for postoperative liver failure.[27,206] Such patients will not decompensate after resection and may achieve a 5-year survival of better than 70%.[27,206] In contrast, the majority of patients with significant portal hypertension will develop postoperative decompensation (mostly ascites),[206] with a 5-year survival of less than 50%. Finally, the survival of those subjects with both adverse predictors (portal hypertension and elevated bilirubin) is less than 30% at 5 years, regardless of their Child–Pugh stage.[27] 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 catheterisation is not necessary. Clinically significant portal hypertension may also be suspected when the platelet count is below 100,000/mm^3 associated with significant splenomegaly.

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%.[27,205,207] The use of intra-operative ultrasonography (IOUS) 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[161] but some authors have challenged the benefits of a safety margin[208] and robust evidence is lacking.

Most groups restrict the indication for resection to patients with single tumor in a suitable location for resection (as shown by triphasic 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,[161] 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.[27,209]

Chemoembolization of the tumor prior to resection offers no benefit.[210] The same is true for the general use of portal vein embolization of the hepatic lobe hosting the tumor[211,212] 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,[27,209,213-216] including recurrence due to dissemination and *de novo* tumors.[217,218] The most powerful predictors of recurrence are the presence of microvascular invasion and/or additional tumor sites besides the primary lesion.[27,209,213-216,219] 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.[217,220] Furthermore, recurrence due to dissemination is more likely to appear during the first 3 years of follow-up.[218] There is no effective adjuvant therapy that can reduce recurrence rates.[221] Preoperative chemoembolization or adjuvant chemotherapy are not effective and may complicate the intervention. Internal radiation[222] and adoptive immunotherapy by activated lymphocytes[223] may have some anti-tumor efficacy but early promising results still have to be properly validated. This is also the case for retinoid administration[224] and interferon therapy.[225,226]

As hoped in all cancers,[227-229] 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.[230-232] However, none of the proposed markers have gained wide acceptance or become routine in clinical practice.[233]

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.[29,216,234] This reflects an advanced tumor stage and there is no evidence that any treatment provides a survival advantage. It has been suggested that patients with recurrence might be candidates for salvage transplantation.[235] 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.[216,218] 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.[236] 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

12. 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).

13. 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.[237,238] 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.[238] These tumors were those that were solitary and smaller than 5 cm. Later experience from France[239] Italy,[193] Spain,[240] 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.[193] 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 maintainance 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.[25,241,242] This has recently fuelled a debate about whether and to what extent the indications for transplantation as therapy for HCC can be expanded.[243] There are very limited data to support extending the selection criteria. 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 understaging, ranging between 10% and 15%.[165,240,244] 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 extrahepatic 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[25,242,245] and this is likely the lowest acceptable survival.[243,246] 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.

The most powerful predictor of recurrence in the absence of extrahepatic spread is macro- or microscopic vascular invasion[30,247] The likelihood of this event runs in parallel to tumor size and number[150,248] 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,[249,250] 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.[27,251] The rate of exclusion on the waiting list may be as high as 25% if the waiting list is longer than 12 months.[251] 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).[27,251] Data from Mount Sinai describe a 50% dropout rate with an even worse survival if the criteria for transplant are expanded.[252] 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.[253] 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 $\leq$3 cm.[254] After implementation it was recognised that too high a priority was given to HCC patients and this was unfair to patients without cancer.[255] 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.[254] 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 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 modelling using published clinical outcomes.[117] Despite some encouraging preliminary data,[248] more recent cohort studies suggest that systemic chemotherapy is ineffective.[256-258] Most groups perform transarterial chemoembolization upon listing because it reduces tumor burden and delays tumor progression.[259] 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 modelling has shown that such intervention is cost-effective if the expected waiting time is longer than 6 months.[117] The main concern with this approach is seeding due to tumor puncture as has been reported for diagnostic biopsy. 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.[260,261]

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.[262]

After the first successful attempt,[263] more than 3000 living donor operations have been performed worldwide using the right hepatic lobe. Results from Asia[264-266] and a recent survey in Japan[267] that includes all the interventions performed suggests that the outcome after live donor transplantation is the same as with cadaveric donation. Interestingly, the value of the Milano 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 straification. 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.[268-271] Decision analysis taking into account the risk of drop-out 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.[272] 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%.[262] 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.

Posttransplant Management

There are insufficient data to support or discourage any specific type of immunosuppression aimed at diminishing the growth of unrecognised 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 reinfection of the graft. There are several effective strategies for hepatitis B,[273] 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.[274] 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.[271,275] 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

14. 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 long enough to allow tumor progression leading to exclusion from the waiting list (level II)./

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

16. 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 centres this is offered as the first therapeutic option.[276] There are no RCT comparing local ablation to resection. Destruction of tumor cells can be achieved by the injection of chemical substances (ethanol, acetic acid, boiling saline) or by modifying the temperature (radiofrequency, microwave, laser, cryotherapy). The efficacy of percutaneous ablation is assessed by dynamic CT 1 month after therapy.[3] 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.[277,278] It is highly effective for small HCC and has a low rate of adverse effects. In addition, it is inexpensive. This should be the standard against which any new therapy should be compared. Ethanol in-

jection 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.[279-282] Long term studies indicate that Child–Pugh A patients with successful tumor necrosis may achieve a 50% survival at 5 years.[28,167,278] 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.[283] 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.[284,285] The efficacy in tumors >2 cm is better than with ethanol.[284-286] RCT have shown that RFA provides better local disease control that could result in an improved survival in RCT.[284-287] 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).[261,288,289] Procedure-related mortality ranges from 0% to 0.3%.[261,288,289] Subcapsular location and poor tumor differentiation have been associated with increased risk of peritoneal seeding[260,261] 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.[290] This manoeuvre 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.

Recommendations

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

18. Alcohol injection and radiofrequency are equally effective for tumors <2 cm. However, the necrotic effect of radiofrequency 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).

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[192] and the only option for which there is adequate and positive information is transarterial chemoembolization.[192]

Systemic chemotherapy with any of the available agents has marginal anti-tumor activity and no impact on survival.[196,291] Despite this lack of efficacy and the associated morbidity, chemotherapy (usually doxorubicin) is frequently administered in conventional clinical practice. Furthermore, it is also sometimes 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.[192,292] Selective radiation through intra-arterial injection of lipiodol-I-131[195,293] or Ytrium-90 labeled microspheres[294] has some antitumor activity but the impact on survival has not been established.

There are multiple other treatment modalities such as octreotide,[200,295] interferon,[296] external radiation,[297] tamoxifen,[192,298-300] or antiandrogenic therapy,[198,199,301] but none have been shown to improve survival.[195,200,293-297,302,303] The first studies testing tamoxifen reported encouraging results[304,305] but unfortunately, larger RCT properly designed, showed unequivocal negative results.[192,298-300] The absence of effect is maintained even when given at high doses[306] and thus, 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,[307] but by megestrol.[308] 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.[150] 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 as 1mm cubes is the most frequently used agent, but polyvinyl alcohol,[309] alcohol,[310] starch microspheres,[311] metallic coils[312] or even autologous blood clots[313] have also been used. Gelfoam powder should be not be used as this may cause biliary damage.[314]

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.[315]

TAE and TACE are considered for patients with non-surgical 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, as this will cause necrosis of the tumor and of the non-tumorous liver deprived of blood supply. This increases 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. 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[316] 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.[192] 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.[3] 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.[3] According to conventional WHO criteria the reported rate of objective responses ranges between 16% and 60%,[192,315] 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.[315]

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 indicate that patient survival is significantly improved.[184] Until very recently, the gain in survival reported in individual trials was not statistically significant.[194,317-319] However, studies performed in Barcelona[320] and Hong Kong[321] 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 improvement in survival in treated patients ranges from 20% to 60% at 2 years,[315] 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.

Recommendations

19. 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).

20. Tamoxifen, antiandrogens, octreotide or hepatic artery ligation/embolization are not recommended (level I). Other options such as radio-labelled Yttrium glass beads, radio-labelled lipiodol or immunotherapy cannot be recommended as standard therapy for advanced HCC outside clinical trials.

21. 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.[17,19,322] 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 relevant 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 $\leq$5 cm with liver function impairment precluding resection. If a long waiting time ($>$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 non-surgical 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 and thus, this is the last effective option in conventional clinical practice.

Patients who present with a more advanced stage because of liver failure or tumor growth with vascular involvement/extrahepatic spread or physical impairment reflected by a markedly impaired performance status ($<$2)[189-191] will not benefit from any treatment option, even one with known efficacy in earlier disease. Accordingly, the optimal policy for these subjects is to attempt to enroll them in research studies testing new agents either within phase 2 investigations or within RCT. The optimal design of such studies should be the comparison of any intervention vs. placebo or the best supportive care as currently practiced. There is no proof that any of the available agents has any impact on survival.

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 non-malignant 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 preclin-

ical stage are 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_action_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.

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