Management of Hepatocellular Carcinoma

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The incidence of hepatocellular carcinoma (HCC) has increased worldwide and is now the 5th most frequent cancer representing approximately 5% of all cancers worldwide. More than 500,000 new cases are diagnosed per year and it is the third cause of cancer-related death and the first cause of death in patients with cirrhosis [1]. The incidence of HCC has major geographical differences, but most patients diagnosed with HCC have underlying cirrhosis. The highest risk is observed in cirrhosis from chronic infection by the hepatitis B virus (HBV) or hepatitis C virus (HCV) [2]. In patients with HCV infection the risk increases with the confirmation of cirrhosis, when the yearly incidence varies between 3-5% and the 5-year cumulative incidence ranges from 15-20% [2]. Since vaccination against HCV is not available, prevention of HCV infection is based on preventing transmission by blood products. Progression from chronic HCV infection to advanced fibrosis or cirrhosis may be prevented in 40% of patients who are sustained responders to new antiviral strategies, such as pegylated interferon and ribavirin [3]. Thus, the prevention of cirrhosis can prevent the development of HCC. On the other hand, in patients with confirmed cirrhosis, the preventive effect of these agents has not been proven [4].

DIAGNOSIS

When cirrhosis has been confirmed, surveillance is the only available strategy to limit tumor-related mortality. If early stage HCC are detected, treatment and cure are possible [2]. Nevertheless, despite surveillance programs, only 30% of HCC are diagnosed at an early stage [1].

A panel of experts organized by the European Association for the Study of the Liver (EASL) proposed surveillance based on abdominal ultrasound (US) and serum alpha-fetoprotein (AFP) every 6 months. Only patients with cirrhosis that could be treated and potentially cured for HCC should undergo surveillance [2]. This includes Child-Pugh A and B patients. Child-Pugh C patients should be evaluated for liver transplantation. If this is not possible, surveillance is a cost-effective choice for early detection and treatment will not improve survival. The following strategy was recommended to diagnose nodules detected by US during surveillance (Figure 1) [2]. If the nodule is <1cm, close follow-up is recommended since less than 50% of the cases are malignant and a reliable diagnosis is not possible with current diagnostic techniques. In 1-2cm nodules, diagnosis of HCC is based on positive cytology or histology. However, false negative biopsies may occur in 30-40% of cases. Thus, a negative biopsy does not clearly exclude malignancy. If the nodule is >2cm and the underlying liver is cirrhotic, diagnosis of HCC can be determined by non-invasive criteria proposed by the EASL experts: two coincident imaging techniques showing a focal lesion >2cm with characteristic arterial hypervascularization, or one imaging technique with a specific pattern associated with AFP >400ng/mL [2]. After detection and diagnosis of HCC the extent of the tumor must be properly staged based on state of the art computed tomography (CT) or magnetic resonance imaging (MRI) [5]. Angiography is not helpful for diagnosis and staging and lipiodol CT is not reliable [2]. Prognosis of HCC depends on the stage of the neoplasm at diagnosis, liver function impairment and the treatment received.

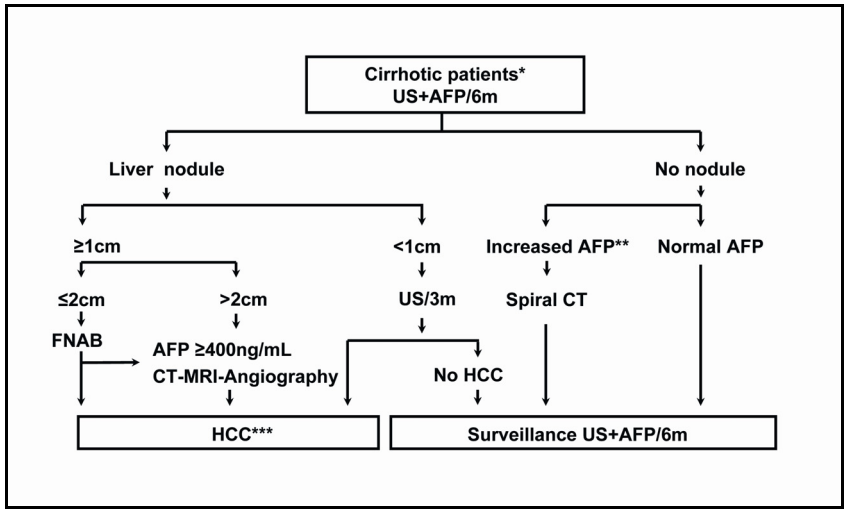

Figure 1: Surveillance and recall strategy for HCC
(reproduced from Bruix et al, J Hepatol 2001 [2], with permission).
FNAB: Fine needle aspiration biopsy.
* Available for curative treatments if diagnosed with HCC.
** AFP levels to be defined.
*** Pathological confirmation or non-invasive criteria.

PROGNOSIS

HCC is generally considered to be a neoplasm with a poor prognosis. However, at present diagnosis occurs earlier; thus certain patients are now successfully treated resulting in an encouraging disease-free survival at 5 years. Nevertheless, prediction of prognosis is still debatable. Several scoring systems exist that divide patients according to expected survival [5]. Almost all of them take into account tumor stage and liver function parameters, but unfortunately predictive accuracy is limited and there is no link between estimated prognosis and treatment indication. Thus, we have developed the Barcelona-Clinic Liver Cancer group (BCLC) staging system which links staging, treatment indication and predicted outcome [5]. With this

system, patients are stratified into four categories (early, intermediate, advanced and end-stage) and the best possible treatment and outcome within each category are established according to specific parameters.

EARLY HCC

The definition of early HCC has varied over time as size limit has steadily decreased; Patients with single tumors ≤5cm or with up to 3 nodules ≤3cm each are usually included. However, pathological and clinical data show that some of these tumors are not early at all, while some are very early HCC or carcinoma in situ (CIS). CIS is a small, very well differentiated HCC with an ill-defined nodular appearance with no invasion of malignant cells in any structure. Cancer invasion and spread (microvascular invasion and satellites) may occur even in tumors <2cm but others are CIS [6]. Both entities may be detected by US, but CIS may be identified if there is no arterial supply as it is a minute, non-arterial enhanced nodule.

The natural history of untreated early HCC is not known because these patients are usually treated. The few available studies report a 65% 3-year survival in Child-Pugh A patients with single tumors [7]. Since survival may exceed 50% at 5 years with proper treatment, effective treatment of early stage HCC is thought to improve patient survival [5]. Effective long-term treatments include surgical resection, liver transplantation and percutaneous ablation.

Surgical Resection

This is the first treatment option in non-cirrhotic patients. However, few cirrhotic patients may receive this treatment [8] because it is limited to those patients with a single HCC ≤5cm and well preserved liver function to prevent morbidity and mortality after resection [5]. Japanese researchers use the indocyanine-green retention rate to identify the best candidates [9], whereas portal pressure and bilirubin are used in Europe. Clinically relevant portal hypertension is defined as the presence of a hepatic vein pressure gradient >10mmHg, esophageal varices and/or splenomegaly with a platelet count $<100x10^9$/L. Patients without portal hypertension and with normal bilirubin have a 70% 5-year survival rate, while those with an adverse profile have 50% or less, even if they are Child-Pugh stage A [5].

The main drawback of surgical resection is tumor recurrence, which may exceed 70% at 5 years [10]. This is the main argument in support of resection instead of transplantation as the first treatment option. Tumor recurrence includes true recurrence secondary to tumor dissemination and *de novo* tumors. Microvascular invasion and the presence of additional nodules or satellites are the best predictors of recurrence due to tumor dissemination [11]. Because of this high recurrence rate these patients are the best patients for evaluation of preventive agents. These include agents that prevent true recurrence such as intraarterial lipiodol-I^{131} or adoptive immunotherapy or those that prevent metachronic tumors such as retinoids or interferons. Nevertheless, despite promising results in randomized studies, all of these substances require further validation before being accepted as standard preventive agents after resection [10].

Liver transplantation

Liver transplantation (LT) is supposed to simultaneously cure the tumor and the underlying cirrhosis if it is limited to carefully selected patients and restrictive criteria. Most groups limit transplantation to patients with single HCC ≤5cm or with up to 3 tumors ≤3cm each. This policy results in a 70% 5-year survival rate with <15% of recurrence during follow-up [5]. Nevertheless, the main concern is the shortage of donors leading to a long waiting time, tumor progression and drop-out from LT. This problem concerns 15% to 50% of enlisted patients depending on the waiting time and has a severe impact on patient survival if outcome is analyzed according to intention to treat [5].

Thus, most programs have established priority policies to decrease the drop-out rate. The United Network of Organ Sharing (UNOS) bases organ allocation on the model for end-stage liver disease (MELD). This model does not give any points to HCC patients who are thus granted a fixed score: patients in stage I (single <2cm) received 24 points and patients in stage II (single 2-5cm or 3 ≤3cm) 29 points. However, this policy unfairly increased the proportion of HCC patients that were transplanted and points were thereafter reduced to 20 and 24 respectively [12].

Living donor liver transplantation (LDLT) using the right hepatic lobe is the most feasible alternative to cadaveric LT and may help overcome the shortage of donors [13]. Analysis of cost-effectiveness

based on the exclusion rate (4% monthly), the morbidity/mortality of donors (0.3-0.5% mortality) and costs has shown that live donation for early HCC in patients enlisted for cadaveric LT is adequate for waiting times of more than 7 months [14].

The availability of LDLT has allowed patients with more advanced HCC to undergo transplantation. The definition of acceptance criteria is a major controversy with critical ethical considerations. In the Barcelona Liver Unit, we have proposed a moderate expansion of criteria to achieve a 50% survival at 5 years: 1) Single HCC ≤7cm; 2) Multinodular HCC with 3 nodules ≤5cm or 5 nodules ≤3cm each; 3) Downstaging to cadaveric criteria by locoregional treatment lasting >6 months [5]. Long-term follow-up will determine whether this strategy is adequate.

Adjuvant therapies (resection, percutaneous ablation, chemoembolization) have also been proposed to reduce tumor progression while waiting for a donor. Since there are no randomized controlled trials (RCTs) in the field, there is no proof of the benefit of these therapies. Cohort studies and cost-effectiveness analysis suggest that there is improved survival if the waiting time exceeds 6 months both for resection and percutaneous treatments [5].

Reinfection of the graft with HCV is a major and unsolved problem in HCV carriers treated by transplantation. It affects almost all patients and leads to cirrhosis in half of them. Antiviral treatments while waiting, during, or after transplantation is only effective in a few patients.

Percutaneous ablation

Percutaneous ablation can be considered for patients with early stage HCC who are not suitable for surgical therapies. HCC foci can be necrosed by the injection of chemical substances (alcohol, acetic acid or hot saline) or by modifying the temperature [radiofrequency (RF), microwave, laser and cryoablation]. Percutaneous Ethanol Injection (PEI) is the gold standard treatment. It is inexpensive, easy to perform and has few adverse events. Complete tumor necrosis (complete response (CR) in oncologic terms) is achieved in 90-100% of HCC <2cm, while the efficacy is reduced as tumor size increases [5]. The best outcome is achieved in Child-Pugh A patients, with a 5-year survival rate of approximately 50% [15]. RF ablation is the most extensively used alternative to PEI. It can be applied percutaneously,

laparoscopically or during laparotomy, and is claimed to result in the same objective responses as PEI, but in significantly fewer sessions [16]. In addition, RF may ablate a 1cm safety margin in surrounding parenchyma and also eliminate satellites. However, there is no evidence that this results in better survival [16]. The side-effects of RF are more severe than those of PEI. For example while tumor seeding is infrequent after PEI, treatment of subcapsular HCC by RF may induce peritoneal dissemination [17] and thus, RF should be avoided in these tumors.

INTERMEDIATE-ADVANCED HCC

Most HCC patients are diagnosed with advanced stage HCC, thus preventing radical treatments. The natural outcome of these patients if left untreated is better known now than two decades ago when patients did not survive any more than 1 year after diagnosis. Nevertheless, modern reported figures of untreated patients in 25 RCTs are extremely heterogeneous with 1- and 2-year survival rates ranging from 10-72% and 8-50%, respectively [18]. This heterogeneity suggests that these patients need to be stratified into separate categories. This was done by our group by joining two control groups of two RCTs in a cohort of 102 patients. Their 1, 2, and 3 year survival was 54%, 40% and 28% and the independent prognostic factors were the presence of cancer-related symptoms (Performance status 1-2) and of an invasive pattern defined as vascular invasion or extrahepatic spread. When patients were divided according to the absence (intermediate stage) or presence (advanced stage) of these prognostic factors the survival at 1, 2 and 3 years was 80%, 65% and 50% vs. 29%, 16% and 8% respectively [19]. This finding is highly relevant when assessing new therapeutic options. Patients are frequently recruited because they cannot receive surgical treatment, but clearly, non-surgical patients represent a very broad spectrum of the disease.

Palliative treatment

These treatments are for patients who cannot undergo radical therapies. Although there is a large list of options that have been tested in patients with HCC, unfortunately the scientific evidence about their use in conventional clinical practice is limited. Since no treatment is

accepted as the standard of care in patients with advanced HCC, the only way to demonstrate an advantage in survival is to perform an RCT comparing active intervention vs. best supportive care. The review of RCTs published in the last 25 years showed 63 trials assessing primary treatments for HCC but only 26 including a control group with conservative treatment [18]. The most extensively evaluated interventions were arterial embolization, with or without chemotherapy, and estrogen blockade. A meta-analytical assessment was possible for both of these techniques, since there are enough trials and patients to obtain robust conclusions. This analysis showed improved survival with transarterial chemoembolization (TACE) in well selected candidates. Accordingly, TACE is now the standard treatment in patients with intermediate stage HCC [18]. In contrast, no improvement in survival was found for tamoxifen [18].

The lack of improved survival with available therapies in patients who are not candidates for TACE, suggests that any new agent proposed for HCC patients should be compared to the best conservative support or placebo. Comparisons with a control arm of a proven inactive treatment such as systemic chemotherapy should not be accepted for scientific and ethical reasons [5].

1. Transarterial embolization

This is the most extensively used treatment for unresectable HCC. Acute obstruction of hepatic artery blood flow nourishing the HCC induces different degrees of tumor necrosis. Gelatin, coils, alcohol, spheres and blood clots have been used to block blood flow and the most common is to inject chemotherapy (doxorubicin, mitomycin and cisplatin are the most usual agents) mixed with lipiodol before arterial obstruction. This treatment induces partial response in 15-55% of patients and delays tumor progression and vascular invasion [18]. Seven RCTs have compared arterial embolization with no treatment [18]. TACE with doxorubicin or cisplatin was assessed in five of them. Only two of them showed significant improvement in survival and in one of them, treatment response was shown to be an independent predictor of survival. Cumulative meta-analysis showed that TACE improved survival compared to no treatment. The data for embolization without chemotherapy were not conclusive due to the few studies and recruited patients. It is important to note that selection of candidates for TACE is critical to avoid side-effects leading to liver failure and death. The optimal candidates have preserved liver

function and asymptomatic multinodular tumors without vascular invasion. Ongoing investigations should define the best chemotherapeutic agents or combinations, as well as the optimal treatment schedule. It is well known, for example, that after extensive necrosis, the tumor is revascularized thus indicating need for new treatment sessions. It has not been clearly established whether treatment should be administered at regular intervals or on a case by case basis and the timing for evaluation of response to treatment and follow-up monitoring requires further studies.

2. Estrogen blockade

Because some HCC present wild or mutant estrogen receptors, antiestrogenic therapy has been tested in patients with advanced disease. Initial studies were encouraging, but large double-blind trials and cumulative meta-analysis of the seven RCTs comparing tamoxifen vs. no treatment failed to show that tamoxifen affected patient outcome [18]. A recent RCT with higher dosage of tamoxifen has also failed to identify any benefit [20], thus confirming that tamoxifen is not active in HCC patients.

Several other treatments such as systemic chemotherapy, internal radiation with lipiodol-I^{131}, proton beam radiotherapy, immunotherapy or octreotide have either been shown to be ineffective or if they have a marginal activity, were only assessed in small sample size studies. Thus, they should not be proposed or should be properly tested to reach enough statistical power to provide solid conclusions [5].

BCLC TREATMENT STRATEGY

Very early stage (Stage 0) or early stage (stage A) HCC patients are candidates for radical treatment. Resection is the first option in patients with single tumors, without clinically relevant portal hypertension and with normal bilirubin. LT is considered in patients with 3 lesions <3cm each or with single tumors <5cm with liver function impairment. If the waiting time is more than 6 months, adjuvant treatments are recommended and LDLT can be considered. Percutaneous ablation is proposed in small non-surgical HCC. Asymptomatic patients with large/multinodular tumors without vascular invasion or extrahepatic spread (Stage B) are candidates for TACE if they have underlying compensated cirrhosis. Patients with advanced tumors (symptomatic and/or invasive pattern) or with

decompensated liver disease (Stage C) can be considered for entry into trials assessing new antitumoral agents. Finally, patients with terminal stage cancer (Stage D) with impaired physical status (Performance status >2) or tumor burden (Okuda stage III) should only receive symptomatic treatment (Figure 2) [5].

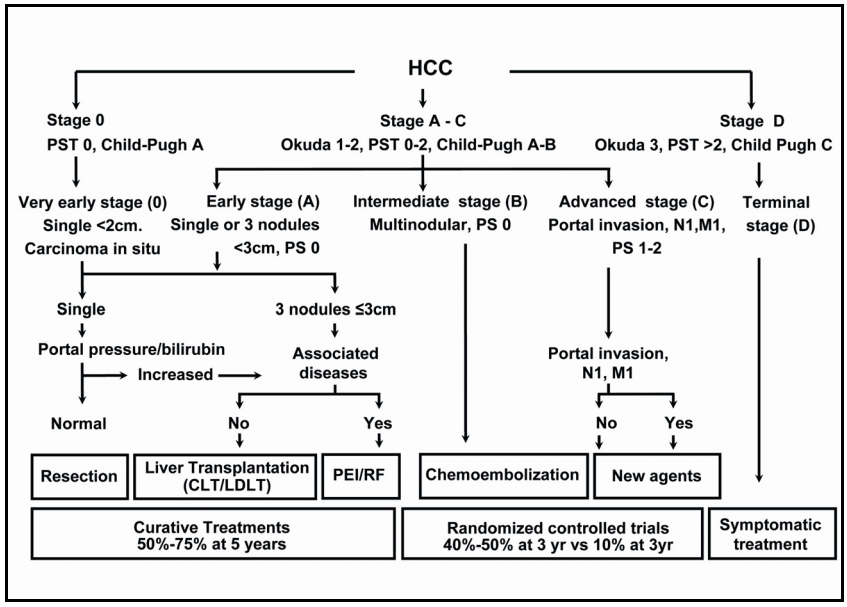

Figure 2: Barcelona-Clinic Liver Cancer (BCLC) staging classification and treatment schedule. Stage 0: Patients with very early HCC are optimal candidates for resection. Stage A: Patients with early HCC are candidates for radical therapies (resection, liver transplantation or percutaneous treatments); Stage B: Patients with intermediate HCC may benefit from chemoembolization; Stage C: Patients with advanced HCC may receive new agents in the setting of RCT; Stage D: Patients with end-stage disease will receive symptomatic treatment. (Llovet JM et al. Lancet 2003 [5]). Reprinted with permission from Elsevier (Lancet 2003, 362, pp 1907-1917).

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