The Barcelona Approach: Diagnosis, Staging, and Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death. It affects mainly patients with cirrhosis of any etiology. Patients with cirrhosis are thus usually included in surveillance plans aiming to achieve early detection and effective treatment. Only patients who would be treated if diagnosed with HCC should undergo surveillance, which is based on ultrasonography and α-fetoprotein every 6 months. Upon diagnosis, the patients have to be staged to define tumor extent and liver function impairment. Thereafter, the best treatment option can be indicated and a prognosis estimate can be established. The present manuscript depicts the Barcelona-Clínic Liver Cancer Group diagnostic and treatment strategy. This is based on the analysis of several cohort and randomized controlled studies that have allowed the continuous refinement of treatment indication and application. Surgical resection is considered the first treatment option for early stage patients. It is reserved for patients with solitary tumors without portal hypertension and normal bilirubin. If these conditions are not met, patients are considered for liver transplantation (cadaveric or live donation) or percutaneous ablation if at an early stage (solitary ≤ 5 cm or up to 3 nodules ≤ 3 cm). These patients will reach a 5-year survival between 50 and 75%. If patients are diagnosed at an intermediate stage and are still asymptomatic and have preserved liver function, they may benefit from chemoembolization. Their 3-year survival will exceed 50%. There is no effective treatment for patients with advanced disease and thus, in such instances, the patients have to be considered for research trials with new therapeutic options. Finally, patients with end-stage disease should receive only palliative treatment to avoid unnecessary suffering. (*Liver Transpl 2004;10: S115–S120.*)

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death.[1] Currently, it is the leading cause of death among cirrhotic patients.[2] The estimates of the burden of this disease for the next decade indicate an increase in the incidence of HCC worldwide. In southern Europe, the age-adjusted incidence rate ranges between 10 and 15 cases per 10^5 inhabitants. HCC arises in a cirrhotic liver due to hepatitis C virus or alcohol abuse in more than 80% of cases, the annual incidence being 3 to 5%.[3] The Barcelona-Clínic Liver Cancer (BCLC) Group, established in the Liver Unit of the Hospital Clínic in Barcelona, is currently diagnosing 250 new HCCs yearly, and several protocols and therapeutic trials are ongoing in this area of research. Our diagnosis and treatment strategy has also been reviewed elsewhere.[4–6]

Surveillance, Recall Policy, and Diagnosis

Surveillance is regularly applied in our unit after the recommendations of the European Association for the Study of the Liver (EASL) panel of experts.[7] In brief, cirrhotic patients are included in surveillance programs, based on the use of ultrasonography and serum α-fetoprotein every 6 months. Only those individuals who would be treated if diagnosed with HCC are enrolled. This includes Child-Turcotte-Pugh (CTP) A patients and CTP B class patients without associated conditions that may preclude radical treatment approaches. CTP C class patients are only considered for transplantation, and thus, there is no rationale to include them in screening programs once this therapy is discarded. Further data is needed to confirm the benefits of other markers, such as glypican-3, protein induced by vitamin K absence (PIVKA), and α-fetoprotein fractions in conventional clinical practice. Applying these programs, about 40% of our patients are diagnosed at early stages and benefit from radical treatments.[5,6] The remaining

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona-Clínic Liver Cancer; RCT, randomized controlled trials; CTP, Child-Turcotte-Pugh; EASL, European Association for the Study of the Liver; PIVKA, protein induced by vitamin K absence; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; PST, performance status test; MELD, model for end-stage liver disease.

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60% of patients are either diagnosed at intermediate stages or have been diagnosed outside surveillance programs in other centers and derived to our unit.

The recall policy proposed by EASL is also prospectively applied. In nodules under 1 cm, which are malignant in less than half of the cases, close follow-up is recommended. In nodules of 1 to 2 cm, HCC diagnosis requires positive cyto-histology. However, there is a 30% to 40% false negative rate with fine-needle biopsy.[8] A negative result, therefore, does not rule out malignancy. In tumors more than 2 cm in diameter, non-invasive diagnostic criteria are applied in cirrhotic patients. HCC diagnosis is established by the concomitant finding of 2 imaging techniques showing a nodule of more than 2 cm with arterial hypervascularization or by a single positive imaging technique showing hypervascularization associated with α-fetoprotein more than 400ng/MI. It has to be pointed out, however, that in our unit a positive histological proof of HCC is required before liver transplantation in all cases. The low risk of fine-needle aspiration biopsy in our center (below 0.01%) favors the balance compared with transplanting a patient with a false-positive result by imaging techniques.[9]

Ultrasonography, spiral computed tomography, and MRI are conventionally used to assess disease extension. Angiography has almost disappeared from the clinical practice in terms of diagnostic and staging purposes. Recent data from our group, comparing computed tomography scan and MRI-angiography with pathological examination of explanted livers suggested that MRI-angiography was more precise than CT scan in the detection of nodules between 1 and 2 cm.[10] Tumors more than 2 cm were diagnosed by both radiological means, whereas HCC less than 1 cm in diameter were only detected in 30% of cases. Therefore, in our clinical practice, we favor MRI-angiography as the more accurate imaging technique. Further studies assessing multirow computed tomography scan or double-contrast MRI are needed to establish the role of these new approaches in the clinical setting.

Staging Systems in HCC

Cancer staging should serve to select the appropriate primary and adjuvant therapy, to estimate the prognosis and also to assist in the evaluation of the results of treatment. HCC patients constitute a particular case in oncology, since their prognosis will rely not only on the tumor stage but also on the underlying liver disease. Cirrhosis underlies HCC in most individuals and thus, their outcome is also related to this entity that simultaneously determines the applicability and efficacy of treatments. It has been considered that appropriate staging systems for HCC should include 4 related aspects: tumor stage, degree of liver function impairment, patient's general condition, and treatment efficacy.[7] Prognostic systems assessing just 1 of these aspects (CTP, TNM, performance status) have a marginal usefulness. The Okuda staging is unable to distinguish between early and advanced HCC and serves mostly to identify end-stage individuals.

Recently, 5 new systems have attempted to overcome these difficulties and aim to establish a useful tumor classification.[4,11–14] The majority of these classifications, however, have been constructed with patients at advanced tumoral stage, and this explains why even patients at supposed early stages achieved poor outcomes [the 3-yr survival rates: French classification stage A[11]: 38%, Cancer of the Liver Italian Program (CLIP) stage 0[12]:50%, Chinese University Prognostic Index (CUPI) stage Low[13]: 25%]. There is currently no HCC classification that is accepted worldwide.

BCLC Staging Classification and Treatment Schedule

The Barcelona-Clínic Liver Cancer (BCLC) staging system was constructed based on the results obtained in the setting of several cohort studies and randomized controlled trials (RCT)s by our group.[4–6] This proposal is not a scoring system since it derives from the identification of independent prognostic factors in the setting of several studies, constituting a staging classification. This classification uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms, and links the stages described with a treatment algorithm. The BCLC classification aims to incorporate prognosis estimation and potential treatment advancements in a single unified proposal (Fig. 1). It has been suggested that it is best suited for treatment guidance, and particularly to select early-stage patients that could benefit from curative therapies.[15] It may be applied to the majority of HCC patients, although individual cases may warrant special consideration, particularly candidates for liver transplantation with impaired liver function.

Patients at a very early stage (Stage 0) and at early stages (Stage A) are optimal candidates for a radical approach. First, they are evaluated for resection if presenting single tumors, absence of clinically relevant portal hypertension, and normal bilirubin. Transplantation is considered in patients with 3 nodules less than 3 cm or with single tumors less than 5 cm with liver function impairment. When long waiting times exist, adjuvant resection or percutaneous treatments are recommended. Living donor liver transplantation can also

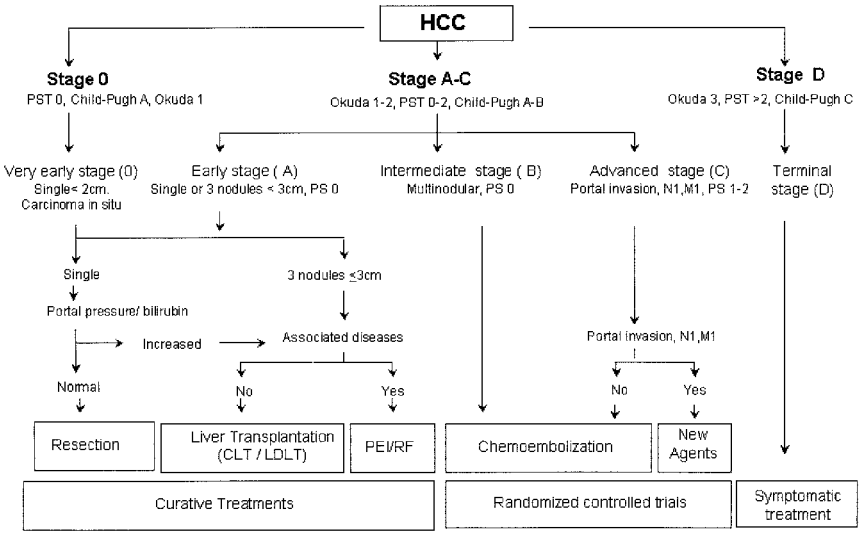

Figure 1. Barcelona-Clinic Liver Cancer (BCLC) staging classification and treatment schedule. Stage 0: Patients with very early HCC are optimal candidates for resection. Stage A: Patients with early HCC are candidates for radical therapies (resection and ablation, liver transplantation; or percutaneous 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 a RCT. Stage D: Patients with end-stage disease will receive symptomatic treatment. (Adapted from Llovet JM et al[6] with permission.)

be considered. Percutaneous treatments, either percutaneous ethanol injection or radiofrequency, are applied in small non-surgical HCC. Asymptomatic patients with multinodular non-invasive tumors (Stage B) are the best candidates for chemoembolization, particularly in CTP A compensated cirrhosis. Patients with advanced tumors (Stage C) showing vascular involvement/ extrahepatic spread or physical impairment, performance status test (PST) = 1–2, are assessed for new antitumoral agents. Finally, patients at a terminal stage (Stage D) with very impaired physical status (PST >2) or tumor burden (Okuda Stage III) receive symptomatic treatment.

Evidence-Based Rationale of the BCLC Treatment Strategy

Prognosis and Treatment of Early HCC

Radical therapies are able to change the natural course of HCC. Evidence for this statement relies on the results of observational studies applying curative treatments (resection, liver transplantation, or percutaneous therapies) in well-selected candidates. The outcomes derived from these studies provide 5-year survival rates above 50% to 70%, a figure by far superior compared with the best natural history of the disease. It is obvious that the natural course of early HCC is unknown, since almost all individuals in this stage are treated.[4–6] In old series, the best survival figures were 65% at 3-years for CTP A patients with single tumors.[16] New series of early untreated patients are unexpected, for ethical reasons.

There are no RCTs comparing any of the 3 major therapies. Recent attempts to compare resection versus percutaneous treatments have failed both in Italy and Japan. Therefore, there is no firm evidence to establish the optimal first-line treatment for small single HCC in patients with well-preserved liver function.[7] Evidence of relative benefit is derived from numerous non-randomized cohort studies. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60–70%),[5,6] and compete as the first option from an intention-to-treat perspective. There is agreement in that transplantation is the best treatment for single tumors in a decompensated cirrhosis or in multicentric small tumors.[5,6]

Resection

Resection of HCC can be performed safely in non-cirrhotic individuals, but this only applies to 5% of cases in the West.[17] Conversely, in patients with cirrhosis strict selection criteria should be applied to avoid complications, such as liver failure.[18,19] The best candidates for resection are patients with single asymptomatic HCC with preserved liver function (BCLC stage A1), which may achieve 70% survival rates at 5

years.[4,6,17–19] Well-preserved liver function has been defined by the absence of clinically relevant portal hypertension (defined as hepatic venous pressure gradient less than 10 mmHg, absence of varices or splenomegaly, and platelet count higher than 100,000/mm^3) and normal bilirubin values.[18,19] In Japan, an indocyanine green clearance at 15 minutes below 20% is used.[20] Following this criteria, only 5% to 10% of the patients in our unit can be resected. In these cases, however, resection is the established first-line option. Outcomes are less favorable in patients with relevant portal hypertension (5-year survival: 50%, BCLC stage A2) or both adverse prognostic factors (5-year survival: 25%,BCLC stage A3).

We have recently incorporated a new stage, the very early HCC stage (BCLC stage 0) defined as patients with well-preserved liver function diagnosed with the carcinoma in situ entity, which mostly involves single HCC less than 2 cm.[6] These patients do not present dissemination. In Japan, these patients show the best outcomes ever published either with resection (5-year survival, 89–93%) or with percutaneous treatment (5-year survival, 71%).[6]

Long-term survival after resection is curtailed by a high recurrence rate (> 70% at 5 years), even in well-selected patients. Pathological predictors of recurrence are microvascular invasion, satellites, and poor differentiation degree.[19] Prevention of tumor relapse has been attempted with internal radiation with Iodine-131, retinoids, and inmunotherapy with promising results. However, the impact of these therapies on survival needs further investigation.[21]

Liver transplantation

Liver transplantation is claimed to be the most effective intervention for HCC patients with cirrhosis since it removes the tumor itself and cures the preneoplastic disease. Optimal candidates for liver transplantation were identified in the 90s: patients with single HCC less than 5cm or with 3 or less than 3 nodules less than 3 cm, without extrahepatic or vascular spread.[19,22] This selection criteria prompts survival rates of more than 70% at 5 years and recurrence less than 15%. However, these outcomes are curtailed as a consequence of tumor progression or death while waiting for a cadaveric donor.[19] Alarming figures of 20% to 50% of drop-out rates have been reported in waiting time exceeding 12 months. Several strategies have been adopted to prevent this problem. In the United States, the United Network for Organ Sharing proposed a new system to allocate patients in the list, according to the model for end-stage liver disease (MELD) score, which has been recently modified. This strategy also gives priority to HCC patients to minimize drop-out rates.[23] Another approach is to apply adjuvant therapies while on the list to prevent tumor progression, such as percutaneous ablation, chemoembolization, or chemotherapy. These treatments are widely used, but their impact on survival is unproved, and future controlled studies are needed. We are applying adjuvant treatments based on cost-effectiveness analysis.[24]

Living donor liver transplantation has emerged as a reasonable alternative to cadaveric liver transplantation for HCC patients. Cost-effectiveness analyses have shown that the benefits of living donor liver transplantation are reached when the waiting time exceeds 7 months.[25] This procedure has already been performed in about 3,000 cases worldwide, but only few series of HCC patients have been reported. The morbi-mortality of the donor is a major concern. Mortality rates are currently estimated to be 0.3% to 0.5%. We are applying living donor liver transplantation for HCC patients with expanded criteria in the setting of a prospective protocol.[5]

Percutaneous treatments

Percutaneous treatments provide good results (5-year survival, 40–50%), but are unable to achieve response rates and outcomes comparable to surgical treatments, even when applied as the first option.[26] Thus, we consider percutaneous ablation as the best option for non-surgical HCC.[4–6] Percutaneous ethanol injection is easy to perform and obtains complete response rates in about 70% of solitary tumors less than 3 cm and in almost 100% in tumors less than 2 cm.[27] Five-year survival in CTP class A patients with small tumors may exceed 60%.[27] Radiofrequency ablation has been claimed to require significantly less sessions than percutaneous ethanol injection to obtain the same response rates and is proposed to better control the local disease.[28] Further RCTs are needed to confirm this statement. For subcapsular tumors, percutaneous ethanol injection is preferred to radiofrequency ablation to prevent needle track seeding.[29]

Prognosis and Treatment of HCC at Intermediate Advanced Stages

The natural course and prognostic factors defining advanced stages are now well-known. The 1- and 2-year survival rates of patients allocated to untreated arms in 25 RCTs were 10% to 72% and 8% to 50%, respectively.[30] This wide range highlights the heterogeneity of the "non-surgical" HCC population and the need to stratify them into separate categories. We re-assessed the natural history of 102 patients from 2 untreated control groups recruited within RCTs.[31] The 1- 2- and

3-year survival rate was 54%, 40%, and 28%, respectively. The independent prognostic factors were the presence of cancer-related symptoms (*Performance Status Test*=1–2) and an invasive pattern, defined as vascular invasion or extrahepatic spread. Patients at intermediate stages (asymptomatic patients, no invasive pattern; BCLC stage B) showed a 1-, 2-, and 3-year survival rate of 80%, 65%, and 50%, respectively, while those with 29%, 16%, and 8% were advanced stages (either symptomatic or invasive pattern, or both; BCLC stage C).

In a recent systematic review of a RCT, we identified about 60 small RCTs published during the last 25 years to assess survival advantages for palliative therapies applied to these HCC populations.[30] Twenty-six studies included a control arm of conservative management, essential to identify survival benefits. These studies analyzed the effectiveness of embolization/chemoembolization, arterial or systemic chemotherapy, internal radiation with Iodine-131, hormonal compounds, immunotherapy, and others. Meta-analysis was performed in 2 areas to assess arterial embolization-chemoembolization and tamoxifen, where enough trials and patients ensured a sample size to obtain robust conclusions. The remaining studies were excluded, either because they compared 2 active anti-tumoral treatments or due to an insufficient sample size to perform a meta-analytic approach.

Arterial embolization

Arterial embolization is the most widely used treatment for unresectable HCC.[30,32–34] In early stages, it may not be indicated as a first-line option, as an outcome review from Japan reports worse results than surgery or percutaneous treatments.[26] Obstruction of hepatic artery induces extensive necrosis in large vascularized HCC. Embolization agents, usually gelatin, may be administered together with selective intra-arterial chemotherapy mixed with lipiodol (chemoembolization). Doxorubicin, mitomycin, and cisplatin are the commonly used anti-tumoral drugs. Arterial embolization achieves partial responses in 15% to 55% of patients,[30] and significantly delays tumor progression and vascular invasion.[32,34]

We performed a meta-analysis of pooled data of 7 RCTs assessing embolization/chemoembolization as a primary treatment of unresectable HCC, in comparison to an untreated control arm.[30] Five studies assessed chemoembolization with doxorubicin or cisplatin. The mean number of treatment sessions ranged between 1 and 4.5 courses. The 2-year survival rate of the treated group was 41% (range: 19–63%), while the control group survival rate was 27% (range: 11–50%). Treatment response assessed 1 to 6 months after the procedure showed objective responses in 35% of the patients (range 16–61%, 108/307). Two studies identified survival benefits favoring treatment,[32,33] and 1 study described a trend.[34] Meta-analysis showed a significant improvement in 2-year survival favoring treatment [Odds ratio: .53; 95% confidence interval: .32–.89, $P = .017$.].

Selection of candidates for chemoembolization is a key point. The benefits of the procedure should not be offset by treatment-induced liver failure. Chemoembolization with doxorubicin (3–4 sessions/year) is recommended in patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread not suitable for radical treatments. By contrast, patients with liver decompensation or hepatic failure (CTP's B-C), should be excluded since the ischemic insult can lead to severe adverse events. The best chemotherapeutic agent or combination of agents, as well as the best treatment schedule, should be determined by further new RCTs comparing 2 active therapies.

Estrogen blockade

The presence of estrogen receptors in advanced HCC was the rationale for anti-estrogen therapy. Particularly, the efficacy of tamoxifen therapy in advanced HCC has been controversial for the last six years. We performed a meta-analysis of 7 RCTS including 898 HCC patients treated by tamoxifen, among which 3 RCTs were double-blinded.[30] One-year survival rate was 23% (range: 2–72%) in treated patients and 22% (range: 0–46%) in control patients. Partial response to tamoxifen was described in 1 patient. Meta-analysis of the RCTs showed no impact of tamoxifen therapy on 1-year survival [Odds ratio: 0.64, 95% confidence interval: .36–1.13] (30). Thus, with the data available, there is no rationale to further assess the usefulness of this treatment in patients with advanced HCC.

Due to the absence of survival benefit with the available therapies in patients that are not suited for chemoembolization, new agents should be compared with the best conservative support or placebo. Comparisons with a control arm of a proven inactive or deleterious treatment, such as systemic chemotherapy, should be discouraged both for scientific and ethical reasons.

Prognosis of Patients at End-Stage Disease

Only a minority of patients are now diagnosed at a terminal stage in our unit. However, this is the rule in areas where surveillance programs are not feasible due to economic or technical reasons, particularly in Asia and Africa. Patients at terminal stages bear a poor prognosis, with less than a 6-month life expectancy and no survival benefit from treatment.[4] Old series characterized these patients as

Okuda stage III, or as Performance Status 3–4. These patients deserve symptomatic treatment.

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