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Review

Updated treatment approach to hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and its incidence will further increase, to reach a plateau in 2015–2020. The natural history of the disease is quite well known, except for its early stages, because the majority of patients at this stage are treated with radical approaches. Staging systems are key to predict the prognostics of patients with cancer, to stratify the patients according to prognostic variables in the setting of clinical trials, and to guide the therapeutic approach. The current knowledge of the disease, however, is not sufficient for recommending a staging system to be used worldwide. The conventional staging systems—Okuda stage, and TNM stage—have shown important limitations for classifying patients. Several new systems have been recently proposed, but only three of them have been validated. The Barcelona Clinic Liver Cancer (BCLC) staging classification links the stage of the disease to a specific treatment strategy. The Japan Integrated Staging (JIS) score has been proposed and used in Japan, although it needs Western validation. The Cancer of the Liver Italian Program (CLIP) score is mainly proposed for patients with advanced tumors. Early detection of HCC through surveillance programs allows the application of potentially curative therapies, such as resection, liver transplantation, and percutaneous ablation in patients with early tumors. The applicability of these treatments varies according to geographical distribution: from 50% to 70% of cases in Japan; 25% to 40% of cases in Europe and the United States; and fewer than 10% in Africa. There are no randomized controlled trials (RCTs) comparing any of the three major therapies. These studies are not feasible in the West. Therefore, there is no firm evidence to establish the optimal first-line treatment for small single HCC in patients with well-preserved liver function. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60%–70%), and compete as the first option from an intention-to-treat perspective. If surgery is precluded, local, nonsurgical therapies are applied. Percutaneous treatments provide good results (5-year survival of 40%–50%), but are unable to achieve response rates and outcomes comparable to those for surgical treatments, even when applied as the first option. Radiofrequency thermal ablation provides slightly better objective response rates than ethanol injection, but no survival advantages have been fully demonstrated. The remaining treatments have been assessed in the setting of around 70 RCTs conducted during the past 25 years. Chemoembolization has been shown to provide modest survival advantages in two RCTs and a metaanalysis, and is currently the mainstay of treatment in 10% of the whole HCC population. The ideal candidates for this option are patients with well-preserved liver function (Child-Pugh class A) and multinodular asymptomatic tumors without vascular invasion. Further RCTs are needed to assess the best chemotherapeutic agent and the ideal re-treatment schedule. There is no firstline option for patients with advanced HCC (vascular invasion, extrahepatic spread, or cancer-related symptoms). Systemic doxorubicin provides partial responses in 10% of cases, without proven survival advantages, and well-known treatment-related complications. Several other treatments, such as immunotherapy, internal radiation, tamoxifen, or antiandrogen agents, have not shown any relevant antitumoral effect or survival benefit. New drugs, such as tyrosine kinase inhibitors and anti-angiogenic agents, are currently being tested in the setting of clinical trials.

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Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide, involving more than half a million new cases yearly.[1] In some areas of Asia and the Middle East, HCC ranks as the first cause of death due to cancer. The incidence of HCC is increasing in Europe and the United States,[2] and it is currently the leading cause of death among cirrhotic patients.[3]

Risk factors

Hepatocellular carcinoma develops in a cirrhotic liver in 80% of patients, and this preneoplastic condition is the strongest predisposing factor.[4] Hepatitis B virus (HBV) infection is the main risk factor in Asia and Africa. Chronic carriers have a 100-fold relative risk for developing HCC, with an annual incidence rate of 2%–6% in cirrhotic patients.[5] Aflatoxin B_1 intake further enhances the risk. In Western countries and Japan, hepatitis C virus (HCV) infection is the main risk factor, together with other causes of cirrhosis.[4,5] Around 20%–30% of the estimated 170 million HCV-infected individuals worldwide will develop cirrhosis. Once cirrhosis is established, the annual incidence of HCC is 3%–5%, and one-third of these patients with cirrhosis will develop an HCC over their lifetime.[3]

Natural history and prognosis

Nowadays it is difficult to approach the natural history of untreated early HCCs. It is obvious that most patients with early tumors are treated by potentially curative therapies, and thus the outcome of untreated individuals is almost impossible to know. The best survival outcomes without treatment are 65% at 3 years for Child-Pugh class A patients with single tumors, whereas, after radical therapies, survival reaches 70% at 5 years.[4] The natural course of advanced HCC is better known. The 1- and 2-year survival rates of untreated patients randomized within 25 randomized controlled trials (RCTs) were 10%–72% and 8%–50%, respectively.[6] Patients included in these studies, however, represent the "best" subset of patients with unresectable HCC. This explains the discrepancies compared with the outcome reported in retrospective series or compared with survival estimates gathered from population-based cancer registries. Patients at terminal stages survive for less than 6 months.[7]

Early stages

The survival of patients with early HCC in referral Liver Units may reach 50% to 70% at 5 years after resection, liver transplantation, or percutaneous treatments.[4] These outcomes are the result of applying the so-called treatment-dependent variables in the selection of candidates, referring to restrictive criteria regarding tumor status and liver function. Tumor status is defined by the size of the main nodule, and multicentricity (single, ≤2 cm; single, 2–5 cm; 3 nodules, ≤3 cm), each of these categories showing significantly different outcomes.[8] In patients with tumors less than 2 cm, recent pathological and clinical data have led to the concept of very early HCC,[4] which correlates with the pathological carcinoma in situ stage.[9] This is a very well-differentiated HCC that contains bile ducts and portal veins, has an ill-defined nodular appearance and, by definition, has not invaded any structure. In Japan, these patients show excellent outcome in terms of survival (resection, 5-year survival, 89%; percutaneous treatment, 5-year survival of 71%) and recurrence (8% at 3 years).[4,10]

Variables related to liver function are relevant in patients not suitable for transplantation. Thus, the absence of clinically relevant portal hypertension, and a normal bilirubin level are key predictors of survival in patients with single tumors undergoing resection.[11,12] Similarly, Child-Pugh class A is the strongest prognostic variable in patients undergoing percutaneous treatments, along with tumor size and response to treatment.[13] Because liver transplantation may potentially cure both the tumor and the underlying liver disease, variables mostly related to HCC have been clearly established as prognostic factors (single tumors ≤5 cm; or three nodules ≤3 cm), defining the so-called Milan criteria.[14]

Intermediate-advanced HCC

The prognosis of HCC was poor when the radical approach was very unlikely in the early 1980s, the median survival figures being less than 1 year.[7,15] Nowadays it is feasible to assess the natural history of HCC at intermediate-advanced stages, from data obtained from patients randomized to the untreated arm in the setting of RCTs. More than 30 trials have been published, including an untreated arm of conservative management, with 2-year control survival rates of 8%–50%.[6] The survivals of a cohort of 102 untreated HCC patients randomized to the control arms of two RCTs run in our Unit were 54%, 40%, and 28%, at 1, 2, and 3 years, respectively.[16] The best predictors of survival were the presence of cancer-related symptoms (performance sta-

tus test [PST]=1–2 or constitutional syndrome) and the identification of an invasive pattern evidenced by the presence of vascular invasion or extrahepatic spread.[16] Thereby, two subgroups with markedly different life expectancies can be identified among patients in an intermediate evolutionary stage. Patients in a truly intermediate stage (asymptomatic patients without a tumoral invasive pattern) showed 1-, 2-, and 3-year survival rates of 80%, 65%, and 50%, respectively, compared with those patients in an advanced stage (at least one adverse prognostic factor), their corresponding figures being 29%, 16%, and 8%, respectively (median survival, 5.8 months). Other predictors of survival described at that stage are Child-Pugh class, ascites, and alpha-fetoprotein (AFP) levels.[7,17]

Endstage HCC

The majority of series published in the 1980s showed a median survival of less than 5–6 months.[15] These patients with endstage disease were characterized by presenting with Okuda stage III, or a PS of 3–4, which reflects severe tumor-related disability. Similarly, advanced tumors in Child-Pugh C patients also account for a very poor prognosis.

Staging classifications in HCC

The knowledge of prognostic factors in HCC patients may aid in the prediction of outcomes and in the design of research investigations, and may provide the basis for a classification of the disease. Prognostic assessment is particularly complex in HCC, considering that variables of two diseases—cirrhosis and cancer—are involved in up to 80% of patients. The key prognostic predictors are only partially known, and vary at different stages of the disease. By contrast with other cancers, the TNM classification is not considered as the gold standard, and more than ten classifications are used throughout the world, with no accepted system worldwide.[4,17–19] The European Association for the Study of the Liver (EASL) panel of experts recommended considering four related aspects to classify HCC: tumor stage, degree of liver function impairment, the patient's general condition, and treatment efficacy.[19] Some of these classifications include variables related to all these items, as summarized in Table 1.

There is no doubt that the limitations of the classical staging systems have already been overcome. The Okuda staging and the Child-Pugh classification might be used as part of any new clinical staging system, but should no longer be used alone. Among the new classifications, however, the heterogeneous survival figures described for the best stages (3-year survival from 80% to 25%) reflect that some studies include mostly patients with advanced disease, with a minor number of effectively treated patients.[20–22] The Chinese University Prognostic Index (CUPI), Cancer of the Liver Italian Program (CLIP), and French staging systems have been constructed with patients at advanced stages.[20–22] They use rough descriptions of tumor stage that are not in accordance with the predictive value of tumor size and multicentricity. For instance, the CLIP score classifies

Table 1. Prognostic variables used in staging systems for hepatocellular carcinoma

	Variables		
Classification	Tumor stage	Liver function	Health status
Okuda stage[15]	50% Liver involvement	Bilirubin Albumin Ascitis	—
French classification[20]	Portal invasion AFP	Bilirubin Alkaline phosphatase	Karnofsky
CLIP classification[21]	50% Liver involvement AFP Portal invasion	Child-Pugh	—
BCLC staging[7]	Portal invasion Metastases Morphology Okuda	Child-Pugh Portal hypertension Bilirubin	PST
CUPI Index[22]	TNM AFP	Ascites Bilirubin Alkaline phosphatase	Symptoms
TNM staging[23]	Morphology Vascular invasion Metastases	Fibrosis	—
JIS score[27]	TNM	Child-Pugh	—

the tumor burden as above/below 50% of liver involvement, thus making it impossible, by definition, to identify patients at early stages.[21] The new TNM, which accords with the American Joint Committee on Cancer (AJCC), is based on series of patients undergoing resection.[23] Pathological information is needed in all cases, this representing a limitation for wide clinical use.

The Barcelona-Clinic Liver Cancer (BCLC) staging system[4,7] was constructed based on the results obtained in the setting of several cohort studies and RCTs by the Barcelona group. This proposal is not a scoring system, because it derives from the identification of independent prognostic factors in the setting of several studies, conforming to a staging classification. This classification uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms, and links the four stages described with a treatment algorithm (Fig. 1). In brief, patients at stage 0, with very early HCC, are optimal candidates for resection. Patients at stage A, with early HCC, are candidates for radical therapies (resection, liver transplantation, or percutaneous treatments). Patients at stage B, with intermediate HCC, may benefit from chemoembolization. Patients at stage C, with advanced HCC, may receive new agents in the setting of an RCT, and patients at stage D, with endstage disease, will receive symptomatic treatment. The BCLC staging system has been validated by several groups in Europe[24] and the United States,[25] and it has been suggested that this classification is best suited for treatment guidance, particularly for selecting early-stage patients who could benefit from curative therapies.[26]

The Japan Integrated Staging (JIS) system is a new scoring system that includes two previous classifications: the TNM, endorsed by the Union Internationale Contre le Cancer (UICC), mostly applied in Japan, and the Child-Pugh classification. A recent validation of the JIS score in more than 4500 patients has shown it to be better than the CLIP score,[27] though it needs to be validated in the West.[25]

Despite some objective advantages of some systems, our current knowledge does not allow us to recommend a staging system to be used worldwide. Several reasons explain the difficulty in identifying the best system to be used worldwide. First, HCC is a complex neoplasm inserted on a preneoplastic cirrhotic liver, and, thus, variables of both diseases leading to death should be taken into account. Second, the disease is very heterogeneous around the world, and this reflects different underlying epidemiological backgrounds and risk factors. Third, HCC is the sole cancer treated by transplantation in a small proportion of patients. Fourth, only around 20% of the patients are currently treated by surgery, thus precluding the wide use of conventional pathology-based systems, such as TNM. Finally, the potential relevance of a molecular signature, identified in terms of outcome prediction, is still unknown.

Unlike breast cancer, lymphoma, and other tumors,[28] no clear biological/genetic markers have shown prognostic value in HCC. In that sense, several human malignant tumors have been recently classified with respect to their prognostic outcome or response to treatment, according to gene expression profiles identified through micro-array technology. Investigators have developed gene-expression-based classifications for breast cancer, non-Hodgkin's B-cell lymphoma, leukemia, lung carcinoma, prostate cancer, bladder cancer, and melanoma. Thus, molecular markers are needed in HCC. However, in order to be clinically useful, the molecular classification should be incorporated into a staging scheme that effectively separates patients in groups with homogeneous prognosis and response to treatment, and thus serves to aid in the selection of appropriate therapy. The potential relevance of a molecular signature, identified in terms of outcome prediction, should ultimately be tested in large cohorts of patients and analyzed together with well-known clinical variables, as has been recently done in breast cancer.[28]

Treatment of hepatocellular carcinoma

Assessment of benefits from treatments

The benefits of treatment should be assessed through RCTs and metaanalyses.[4,6] Other sources of evidence, such as nonrandomized clinical trials or observational studies, are considered less robust. RCTs should be conducted when there is uncertainty of the final outcome comparing two arms. No such approach is justified, however, if the results obtained in the setting of cohort studies are clearly better compared with the natural course of the disease. This is the case for the so-called radical or curative treatments, such as resection, liver transplantation, and percutaneous treatments as therapies of early tumors, which provide survival rates better than their untreated counterparts (5-year survival rates of 40%–70% vs <20%). Long-term outcomes of the main series are depicted in Table 2.

The remaining treatments have been assessed in the setting of around 70 RCTs conducted during the past 25 years.[6] These treatments have been called palliative, because they are aimed to delay the progression of the disease, rather than to cure the tumor itself. Ideally, the primary endpoint of these studies should be overall survival or cancer-specific death. Other endpoints used are tumor response rate, time to progression, and quality of life. In these studies, only chemoembolization has been shown to improve survival in around 10% of the whole

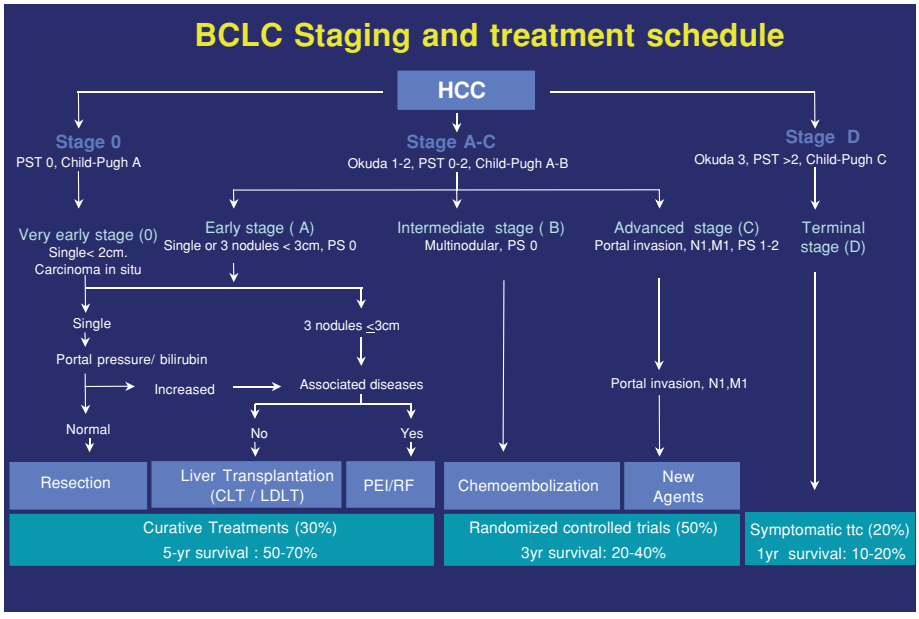

Fig. 1. Barcelona Clinic Liver Cancer (*BCLC*) staging classification and treatment schedule. *Stage 0*, Patients with very early hepatocellular carcinoma (*HCC*) are optimal candidates for resection. *Stage A*, Patients with early HCC are candidates for radical therapies (resection, liver transplantation, 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 randomized controlled trials (RCTs). *Stage D*, Patients with endstage disease will receive symptomatic treatment. *PST*, performance status test; *CLT/LDLT*, cadaveric liver transplantation/living-donor liver transplantation; *PEI/RF*, percutaneous ethanol injection/ radiofrequency thermal ablation; *ttc*, treatment; *yr*, year. Modified from Llovet et al.,[4] with permission

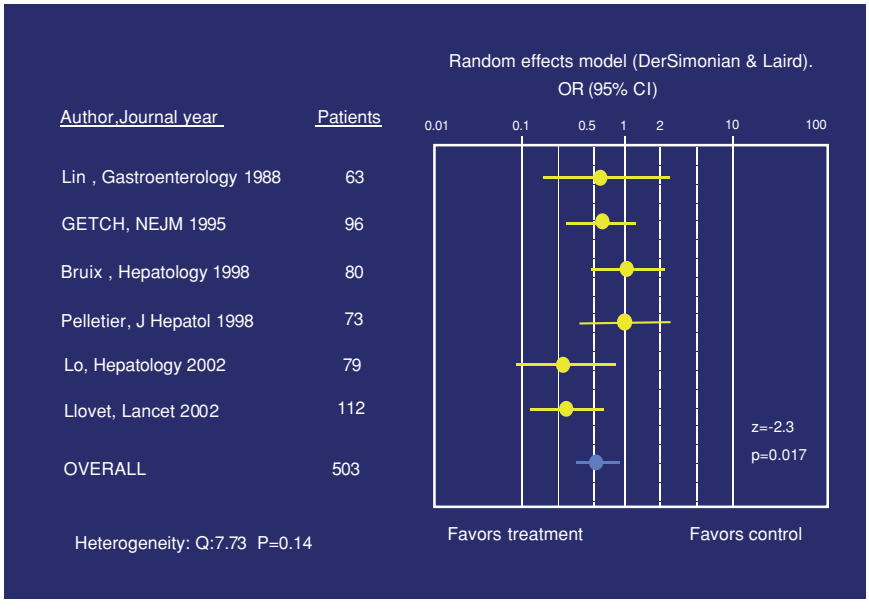

Fig. 2. Metaanalysis of RCTs comparing 2-year survival of chemoembolization/ embolization vs conservative management for unresectable HCC. Random effects model: odds ratio (*OR*), 0.53 (95% confidence intervals [CI], 0.32–0.89; $P = 0.017$). *NEJM*, *New England Journal of Medicine*. Reproduced from Llovet and Bruix[6], with permission

HCC population.[6,29] Internal radiation and intraarterial chemotherapy provide promising results, but without any proven impact on survival. Tamoxifen does not provide survival advantages. Clinical data assessing new generations of drugs such as cytostatic agents, immunomodulators, or gene therapies are still scarce.

Curative treatments

Surgical resection

Surgery is the mainstay of HCC treatment. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60%–70%), and

compete as the first option in patients with early tumors, from an intention-to-treat perspective.[11] Resection yields good results (5-year survival of 60%–70%) in candidates who present with single tumors and excellent liver functional reserve. Japanese authors use the indocyanine green (ICG) retention rate to identify the best candidates,[10,30] while portal pressure and bilirubin are the parameters used in Europe.[11,12] Clinically relevant portal hypertension is defined as the presence of either an hepatic vein pressure gradient of more than 10 mmHg, esophageal varices, or splenomegaly with platelet counts of less than 100 000/mm^3.[11]

Tumor recurrence complicates 70% of patients at 5 years, as is predicted by the presence of microvascular invasion, poor histological differentiation, and satellites.[11,31] Preventive strategies assessed in RCTs have been recently reviewed.[32] Adjuvant chemoembolization or chemotherapy did not add benefit, while internal radiation with I-131[33] and interferon[34] showed promising results. Adoptive immunotherapy by activated lymphocytes reduced recurrence in a trial with 150 patients,[30] and a similar effect was described with retinoids in an RCT with 89 patients.[35] None of these results have been reproduced in large series, and they need thorough validation.

Liver transplantation (LT). The clinical impact of LT has changed the treatment strategy for HCC, particularly in the West. In well-selected candidates, this treatment may potentially cure the tumor and the underlying cirrhosis at the same time. However, the role of LT in the management of HCC has evolved throughout three different periods.

During the 1980s, the high recurrence rates (32%–54%) and poor outcomes (5-year survival, <40%) obtained from transplant registries were related to the acceptance of patients with exceedingly advanced tumors with adverse prognostic factors such as macroscopic vascular invasion, lymph node involvement, and extrahepatic spread at the time of the procedure.[36,37] These devastating figures led to questioning of the indication of LT for HCC in some programs. The initial experiences, however, served to demonstrate the feasibility of the operation and to establish the criteria to avoid a very aggressive and expensive treatment in patients with no hope of long-term survival. During the early 1990s, a second era of LT for HCC was faced. Analysis of the previous experience suggested that patients with minute or incidental asymptomatic tumors discovered at the time of transplantation had the same outcome as patients with nonmalignant disease. Some pioneering groups selecting the "optimal candidates"—patients with a single HCC of 5 cm or less, or up to three nodules of 3 cm or less—reported a 70% 5-year survival, with a recurrence rate below 15%.[11,14,38,39] During this period, LT was considered in most centers as the firstline option for early HCC. Years later, the United Network for Organ Sharing (UNOS) of the United States adapted this definition to provide priority to HCC patients listed for liver transplantation.

A thorough analysis of the reported outcomes led to the knowledge that only vascular invasion, or its surrogate markers—such as degree of poor differentiation—were able to alter the prognosis of well-selected candidates by causing recurrence in a minority of patients.[11,40] In addition, the TNM classification was questioned as an efficient tool for HCC staging prior to LT, and it became a marginal staging system in clinical practice.[41] At this point, the ideal candidates for LT were already recognized, and a common agreement was that patients should only be listed for LT when the probability of living for 5 years after the procedure exceeded 50%.[42]

At present, a new situation is faced, with two opposite driving forces in the field. First, evidence that the shortage of donors has led to extremely long waiting times in almost all countries has distorted the outcomes reported when analyzed according to intention to treat.[11] We first reported the impact of dropout on overall survival in HCC patients listed for LT,[11] and these results have been confirmed by other groups.[43] In our study, dropout rates above 20% in waiting times exceeding 6 months led to alarming survival figures according to intention-to-treat analysis (around 60% at 2 years). Several strategies have been proposed to ameliorate the impact of tumor progression while a patient is waiting for a donor. First, adjuvant therapies—percutaneous ablation, chemoembolization, or even chemotherapy—during the time on the waiting list have been assessed in the setting of observational studies.[44,45] At present, there is no evidence of survival benefit for these procedures, and, thus, randomized studies are needed to assess whether neoadjuvant therapies might decrease the dropout rate or prevent recurrences after transplantation.[4]

Second, increasing numbers of studies are proposing that the expansion of the conventional criteria may not adversely impact survival.[43] The standard selection criteria for cadaveric LT rely upon a strict size limitation. These criteria have recently been questioned, and some groups are proposing extended indications for HCC. Given the current information available, there are no compelling scientific data for expanding the accepted criteria for cadaveric LT in HCC. The proposals for expansion are based on explant examination, and, up to now, no imaging techniques have been shown to have the same diagnostic accuracy as pathology. If the University of California San Francisco (UCSF)[43] and Pittsburgh[46] definitions were to be applied to radiological reports, then we would surely list patients with

Table 2. Survival rates of patients with HCC according to treatment[a]

Treatment	*n*	Survival 1-year	Survival 5-year
Surgical resection			
Fong et al., 1999	100	83%	42%
Llovet et al.,[11] 1999	77	85%	51%
No portal HT, normal bilirubin	35	91%	74%
Takayama et al.,[30] 2000	74	100%	62%
Arii et al.,[8] 2000			
Stage I, HCC <2 cm	1318	96%	72%
HCC 2–5 cm	2722	95%	58%
Stage II, HCC <2 cm	502	92%	55%
HCC 2–5 cm	1548	95%	58%
Wayne et al.,[40] 2002	249	83%	41%
Liver transplantation			
Mazzaferro et al.,[14] 1996	48	84%	74%*
Bismuth et al.,[39] 1999	45	82%	74%
Llovet et al.,[11] 1999	87	84%	69%
Jonas et al.,[38] 2001	120	90%	71%
Percutaneous ethanol injection			
Livraghi et al.,[51] 1995			
Child A, HCC ≤5 cm	293	98%	47%
Child B, HCC ≤5 cm	149	93%	29%
Arii et al.,[8] 2000			
Stage I, HCC <2 cm	767	96%	54%
HCC 2–5 cm	587	95%	38%
Stage II, HCC <2 cm	426	92%	33%
HCC 2–5 cm	483	87%	28%
Radiofrequency ablation			
Rossi et al., 1996	39	94%	40%
Buscarini et al., 2001	88	89%	33%

Arterial embolization and chemoembolization	*n*	Survival 1-year	Survival 2-year
GETCH,[59] 1995; chemoembolization (cisplatin)	50	62%	38%
Bruix et al.,[62] 1998; embolization+ coils	40	70%	50%
Pelletier, 1998; chemoembolization (cisplatin)	37	51%	24%
Llovet et al.,[29] 2002			
Embolization	37	75%	50%
Chemoembolization (Adriamycin)	40	82%	63%
Arterial chemotherapy (Lipiodolization)			
Kawai, 1997			
Arterial Lipiodolization (epidoxorubicin)	208	70%	45%
Arterial Lipiodolization (doxorubicin)	207	73%	55%

Modified from Llovet et al.[4]

unidentified more advanced tumor stage in whom understaging would have an impact. These series lack informative data on dropout rates and intention-to-treat survival and overall survival for the specific group of patients in whom expanded criteria are applied. Only one series of cadaveric LTs, from Mt. Sinai School of Medicine reported specific outcomes for patients with expanded criteria (5-year survival, 44%; 5-year intention-to-treat survival, 25%).[47] As we recently suggested, the proposed expanded tumor stage for liver transplantation should perhaps become the criterion for exclusion from the waiting list because of tumor progression.[42]

The results of expanded indications with living-donor LT (LDLT) have been recently reviewed elsewhere.[48] In the largest series published up to now, including 316 patients from Japan who underwent LDLT for HCC, the 3-year survival was significantly lower for patients outside the Milan criteria when compared to those within the limits (60% vs 79%, respectively).[49]

Percutaneous treatments

Percutaneous treatments are currently considered as minimally invasive procedures, and constitute the best

medical option for nonsurgical HCC.[4] Tumor ablation is achieved by modifying the temperature of neoplastic cells (radiofrequency, microwave, laser, and cryoablation) or by using chemical substances (alcohol, acetic acid). Percutaneous ethanol injection (PEI) has been used as a primary treatment of HCC during the past 20 years, initially in Japan, and afterwards throughout the world.[13,50–52] Even nowadays it is used as the firstline option for early tumors in some centers.[8] Initial complete response (CR) rates decrease directly with tumor size, and CR rates are 95% and 70% for tumors of 2-cm and 3-cm diameter, respectively.[13] Additional factors, reflecting poor biological behavior, have been related to poor response rates, such as the degree of differentiation (poor differentiation is a predictor of failure)[53] and the radiological characteristics of the lesions (infiltrative vs nodular tumors).[54] The assessment of response requires particular attention, because no homogeneous criteria are applied worldwide, and this may lead to misleading conclusions. Currently, at least three criteria are used. The WHO criteria mainly take into account the measurement of areas,[55] with the EASL amendment measures of the WHO criteria taking into account the area with viable tumor (reflected by hypervascularization in the arterial phase[19]), while the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, endorsed by the National Cancer Institute of the United States, have been proposed, which take into account plane diameters.[56]

The best results obtained in series of HCC patients treated by percutaneous ethanol injection provide 5-year survival rates of 40%–50%. Independent predictors of survival are the Child-Pugh score, serum albumin, and platelet count (reflecting liver functional impairment); the number or size of nodules; and the baseline alpha-fetoprotein levels (reflecting tumor stage).[13,54] Thus, the best outcomes have been reported in Child-Pugh A patients with small single tumors, commonly less than 3 cm in diameter.[13,50–52] Recently, we have identified that the initial CR is an independent predictor of survival, thus presenting the strongest evidence supporting the idea that CR may lead to survival advantages.[13]

Radiofrequency (RF) ablation constitutes the most extensively used alternative to PEI, either through single or multiple cooled-tip electrodes, or a single electrode associated with J-hook needles, according to different equipment available. RF can be applied percutaneously, laparoscopically, or during laparotomy. Recently, two RCTs claimed that RF achieved slightly better response rates, with a significantly lower number of sessions, and with better local control of the disease,[52] and improved prognosis compared with PEI.[57] However, robust survival advantages have not been proved yet for RF.

The remaining percutaneous treatments have been addressed in a few series, mostly coming from Asia. Other therapies are either associated with a high rate of complications (cryoablation), have not been proven to present any advantage (microwave coagulation, laser therapy), or are still experimental.[4]

Palliative treatments for HCC

The majority of patients diagnosed in the West present with tumors at intermediate-advanced stages, where potentially curative treatments have failed to provide reasonable results.[2–4] In the HCC field, there are no mega-trials including more than 1000 patients, which are considered the "best source of evidence". These studies are very expensive and require a well-organized network of expert centers, along with a strong endorsement by the industry. Similarly, there is no single metaanalysis of individual data assessing any treatment for HCC. As described below, only one area may warrant this approach—chemoembolization—and the efforts to gather all the information have failed up to now. Thus, the majority of treatments have been assessed in the setting of the so-called small RCT.[6]

We have recently reviewed the evidence obtained from RCTs published in English in peer-reviewed journals during the past 25 years.[6] Sixty-three RCTs were identified assessing primary treatments of HCC, and 26 studies included a control arm of conservative management, essential to identify survival benefits. Few additional RCTs have been reported since this publication. These studies analyzed the effectiveness of embolization/chemoembolization, arterial or systemic chemotherapy, internal radiation with 131-I-labelled Lipiodol, hormonal compounds, immunotherapy, and others. Metaanalysis was performed in two areas, arterial embolization and tamoxifen, where enough trials and patients ensured a sample size sufficient to obtain robust conclusions.

Arterial embolization and chemoembolization

Arterial embolization is the most widely used primary treatment for unresectable HCC, and in this setting is aimed to increase survival.[29,58] In early stages, it may not be indicated as the firstline option, as an outcome review from Japan reports worse results than those for surgery or percutaneous treatments.[8] Obstruction of the hepatic artery induces extensive necrosis in large vascularized HCC. Embolization agents—usually gelatin—may be administered together with selective intraarterial chemotherapy, mixed with Lipiodol (chemoembolization). Doxorubicin, mitomycin, and

cisplatin are the commonly used anti-tumoral drugs.[58] Arterial embolization achieves partial responses in 15%–55% of patients,[4,6,58] and significantly delays tumor progression and vascular invasion.[29,59]

Seven RCTs including a total of 516 patients have compared embolization with conservative management, five of which have assessed chemoembolization with doxorubicin or cisplatin.[6] Survival benefits were identified in two studies,[29,60] one of which identified treatment response as an independent predictor of survival.[29] Metaanalysis showed a beneficial survival effect of embolization/chemoembolization in comparison to the control group (Fig. 2). Overall, this effect may be considered modest, as is expected to occur in advanced neoplasms. Survival benefits were not identified with embolization alone, but the number of individuals analyzed is still low. There is no good evidence for the best chemotherapeutic agent and the optimal retreatment strategy. The two positive RCTs applied three to four treatments per year, using doxorubicin and cisplatinum, respectively .

The benefits of chemoembolization should not be offset by treatment-induced liver failure. Predictors of outcome are related to tumor burden (tumor size, vascular invasion, and AFP levels), liver functional impairment (Child-Pugh, bilirubin, ascites), health status (Constitutional Syndrome [Sd], Karnofsky index, PST), and response to treatment.[29,58–60,62] In fact, most of the RCTs include Child-Pugh A patients (70%–100%) with multinodular HCC without vascular invasion (overall, >95%). Thus, the best candidates are patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread,[6,29] while patients with liver decompensation or hepatic failure (Child-Pugh B-C), should be excluded, because the ischemic insult can lead to severe adverse events.[59] Heterogeneity in the selection of candidates may result in opposite results, and thus should be taken into account when designing and analyzing RCTs. The publication of new trials is encouraged, because these are needed to refine the selection of the target population and to establish the best chemotherapeutic agent and the optimal treatment schedule.

Several issues remain to be elucidated, however, to better understand the benefits of chemoembolization in the HCC population.[58] First, which is the best embolization agent and chemotherapeutic drug, and how can the intratumoral concentration of the drug (and thus, its efficacy) be increased. Second, which is the best treatment scheme for repeat treatment, and should it be done at fixed timing or upon disease progression after the initial response.[58] Third, is there an additive or synergistic effect between arterial embolization and chemotherapy, and, if so, is chemoembolization better than embolization alone.[58] And, finally, do the modest survival advantages already identified require further studies to increase the strength of the evidence.[58]

Arterial chemotherapy (direct arterial administration of chemotherapy, or administration using pumps) or Lipiodolization (arterial administration of Lipiodol—no antitumoral activity—or a mixture containing Lipiodol as a vehicle for chemotherapy) should be analyzed separately from chemoembolization, because they are not expected to achieve arterial occlusion.[58] Target chemotherapy for liver cancer, using Lipiodol as a vehicle for chemotherapy was called "Lipiodolization" by Kanematsu et al.,[61] and has been related to objective responses of 10%–25%, but has shown no survival advantage.[58] Apoptosis may be evident after these treatments .

Other treatments

The presence of estrogen receptors in advanced HCC was the rationale for anti-estrogen therapy. Metaanalysis of seven RCTs, comparing tamoxifen with conservative management, comprising 898 patients, showed neither an anti-tumoral effect nor a survival benefit of tamoxifen.[6,63] Thus, this treatment is discouraged in advanced HCC. Other hormonal compounds, such as megestrol or anti-androgens, have failed to provide a robust survival advantage to date.

RCTs assessing other primary treatments for HCC have been reviewed elsewhere.[6] Overall, none of them have resulted in a proven advantage in terms of survival. However, some strategies provide objective response rates above 20%, as is the case of internal radiation with 131-I-labelled Lipiodol[35] or arterial Lipiodolization (chemotherapeutic agents and Lipiodol).[38] These treatments deserve further analysis, because the RCTs available up to now are either not powered to identify minor survival advantages or they include another potentially active control arm, precluding the identification of advantages, if present. Systemic chemotherapy with doxorubicin has been tested in the setting of clinical trials in more than 1000 patients, and induced objective responses in 10% of patients as a single agent and in up to 26% when used in combination with other agents (platinum, interferon, adryamicin and fluorouracil [PIAF] regimen). The potential benefits of these treatments are offset by the unacceptable incidence of adverse events.[64] The encouraging results of initial trials with interferon and octreotide have not been reproduced by others. Improvements in the knowledge of the molecular pathogenesis of HCC[65] have led to the testing of some cytostatic agents that may interact upon some disrupted pathways. Phase I/II/III studies are currently being conducted to disclose whether epidermal growth factor receptor inhibitor, platelet-derived growth factor (PDGF) receptor inhibitors, and antibodies against vascular en-

dothelial growth factor (VEGF), among others, may have a role in the treatment of this neoplasm. Even further from the bedside are the results of gene therapy in HCC patients with advanced tumors, which have been awaited during the past few years.

Treatment strategies

The treatment strategies for HCC vary throughout the world. Several differences in the treatment approach are due to geographical differences in the incidence and presentation of the disease. However, the main reason for the differences in approach is that there are only fewer than 100 RCTs in the field able to provide a rational therapeutic approach to this neoplasm. Several treatment guidelines have been published.[4,66,67] The BCLC staging system links tumoral stage with a treatment strategy, and aims to incorporate prognosis estimation and potential treatment advances in a single unified proposal[4,7] (Fig. 1). It may be applied to the majority of HCC patients, although individual patients may warrant special consideration, particularly candidates for cadaveric LT with impaired liver function. Patients at a very early stage (stage 0) are optimal candidates for a radical approach. Patients at early stages (stage A) are evaluated for resection if presenting with single tumors, absence of clinically relevant portal hypertension, and normal bilirubin. Transplantation is considered in patients with three 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 be considered. Percutaneous treatments, either PEI or RF, are applied in small nonsurgical HCC. Asymptomatic patients with multinodular noninvasive tumors (stage B) are the best candidates for chemoembolization, particularly those with Child-Pugh A compensated cirrhosis. Patients with advanced tumors (stage C) showing vascular involvement/extrahepatic spread or physical impairment (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 3) receive symptomatic treatment.

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