Review Article

Management of hepatocellular in the United States

Ali A. Mokdad[1], Caitlin A. Hester[1], Amit G. Singal[2], Adam C. Yopp[1]

[1]Department of Surgery, Division of Surgical Oncology, [2]Department of Internal Medicine, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390, USA

Contributions: (I) Conception and design: AA Mokdad, AC Yopp; (II) Administrative support: AA Mokdad, AC Yopp; (III) Provision of study materials or patients: AA Mokdad, AC Yopp; (IV) Collection and assembly of data: AA Mokdad, AC Yopp; (V) Data analysis and interpretation: AA Mokdad, AC Yopp; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Adam C. Yopp. Department of Surgery, Division of Surgical Oncology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390, USA. Email: adam.yopp@utsouthwestern.edu.

Abstract: Hepatocellular carcinoma (HCC) is a major cause of cancer burden globally. In the United States, the incidence of HCC is forecast to continue to rise for the next 15 years. Patients with HCC vary markedly owing to heterogeneous tumor characteristics and concomitant liver dysfunction. In the United States and Europe, HCC is staged and managed according to the Barcelona Clinic Liver Cancer (BCLC) system. For very early and early stage HCC, or BCLC 0/A, liver transplant is the optimal treatment option. Liver resection and radiofrequency or microwave ablation are alternative treatment options. For intermediate stage HCC, or BCLC B, transarterial chemoembolization (TACE) is the standard of care. An alternative locoregional therapy, transarterial radioembolization using yttrium-90, has shown comparable outcomes with TACE and may be used in patients for whom TACE is contraindicated. For advanced stage HCC, or BCLC C, systemic chemotherapy with sorafenib, a multikinase inhibitor, is the only evidence-based treatment option available. Another multikinase inhibitor, regorafenib, was recently approved as a second-line therapy for this patient group. Randomized clinical trials investigating other agents in enriched patient groups and novel therapeutics including checkpoint inhibitors are underway. Patient with prohibitive performance status and/or end stage liver dysfunction are classified terminal stage HCC, or BCLC D, and are managed with best supportive care. The future direction for the management of HCC will rely on continuing efforts to uncover molecular pathways and actionable genetic aberrations in HCC.

Keywords: Liver neoplasms; Barcelona Clinic Liver Cancer (BCLC); liver transplantation; ablation techniques; therapeutic embolization; chemotherapy

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Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer burden globally. In several countries in Asia, HCC is the most common cause of cancer deaths (1). In Europe, the number of new HCC cases has increased dramatically over the past two decades (2). Incident HCC cases have almost doubled during the same period in the United States, and are forecasted to continue to rise over the next 15 years (3).

The majority of patients with HCC have underlying chronic liver dysfunction and/or liver cirrhosis (4). The cause of liver dysfunction is dependent on incident geographic region, and is mainly related to chronic hepatitis B or C, alcohol abuse, or non-alcoholic fatty liver disease (5). The concomitant liver dysfunction and tumor burden further complicate the HCC treatment paradigm influencing decision-making and ultimately patient prognosis. The challenge lies in delivering curative and life-prolonging treatments without negatively impacting the underlying liver dysfunction thus causing hepatic decompensation. A multidisciplinary treatment approach encompassing the

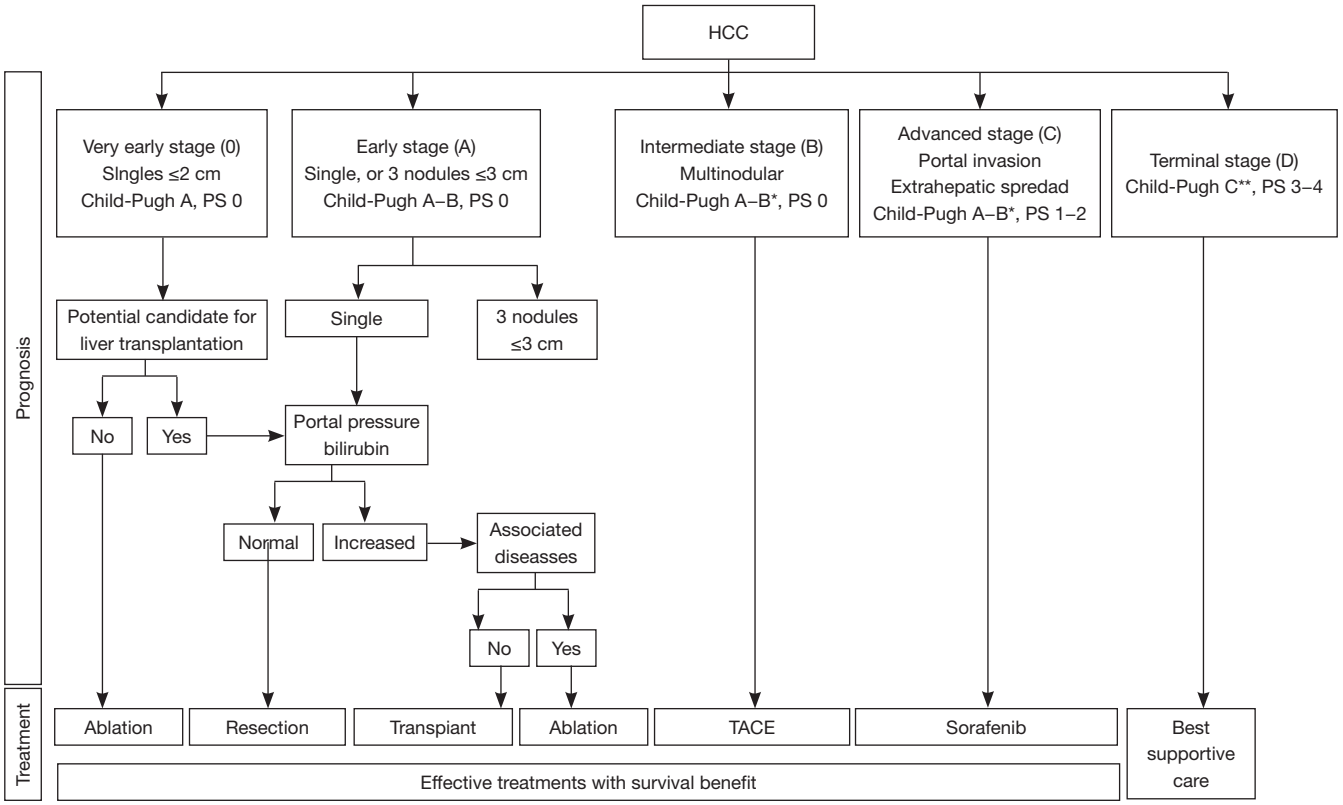

Figure 1 Staging and treatment of hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer system. Reprint from Gastroenterology, Volume 150, Issue 4, Jordi Bruix, Maria Reig, Morris Sherman, "Evidence-Based Diagnosis, Staging, and Treatment of Patients with Hepatocellular Carcinoma", April 2016, with permission from Elsevier. *, Child-Pugh classification is not sensitive to accurately identify patients with advanced liver failure that would deserve liver transplant consideration; **, patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enlistment criteria. PS, performance status.

specialties of surgery, oncology, hepatology, radiology, and palliative care is needed to bridge the gap between liver function and tumor biology to ensure appropriate HCC treatment decisions. Our group and others have demonstrated the benefits of a multidisciplinary approach to HCC care in terms of improved patient outcomes (6-8).

The Barcelona Clinic Liver Cancer (BCLC) algorithm is an externally validated staging system providing a framework for the management of HCC, and has been adopted by the European Association for Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) (9-11). In the BCLC staging system, treatment is based on tumor burden, liver function, and Eastern Cooperative Oncology Group (ECOG) patient performance status (PS) (*Figure 1*). Patients with preserved liver function and low tumor burden (BCLC 0 and A) are amenable to curative treatments, whereas those with poor liver function (Child Pugh C) and/or prohibitive performance status (PS >2) are limited to supportive care only (BCLC D). In the middle of these two extremes of the HCC staging and treatment spectrum is a group of patients with both large tumor burden and preserved liver function for whom palliative treatment options are appropriate.

The aim of this review is to discuss current HCC treatment paradigms according to the BCLC staging system and to highlight emerging novel therapies.

BCLC 0 and A

BCLC A, or early stage HCC, includes patients with low

tumor burden—specifically, a solitary lesion or up to three nodules smaller than 3 cm—with preserved liver function and performance status. Patients with a single nodule smaller than 2 cm constitute very early stage HCC or BCLC 0.

Treatment for patients with very early and early stage HCC is curative, and comprises tumor ablation, liver resection, or orthotopic liver transplant. To date, however, the data guiding the choice of treatment is inconclusive and is largely dependent on patient comorbidities and institutional preference or resources.

Liver resection and radiofrequency ablation (RFA) for early stage HCC have been compared in three randomized clinical trials, each reporting dissimilar results. Two trials demonstrated similar 3-year overall survival (OS) and recurrence-free survival (RFS) between liver resection and RFA (OS: 73–75% *vs.* 67–69%; RFS: 61–69% *vs.* 50–60%, P value not significant for both comparisons) (12,13), whereas the third showed improved overall and recurrence-free survival at five years in the resection group (OS: 92% *vs.* 70%, P<0.01; RFS: 61% *vs.* 46%, P=0.02) (14). The varying results may be explained in part by differences in tumor size across the three trials, since efficacy following radiofrequency ablation correlates to tumor size (15).

Comparative studies according to tumor size in patients with early stage HCC failed however to provide consistent evidence favoring RFA or liver resection based on size. In patients with a single HCC nodule smaller than 2 cm, several observational studies demonstrated similar overall survival between RFA and liver resection (16-18). For HCC lesions greater than 2 cm (and up to 5 cm), liver resection was associated with similar overall survival in some studies, and better overall survival in others, compared to RFA (13,14,19-21). Patient and tumor characteristics in these observational studies (and a subgroup analysis in two randomized trials) were dissimilar between the two treatment groups; patients undergoing RFA were more likely to be older, a more advanced Child-Pugh class, and have lower platelet counts.

Given the limitations of RFA to achieve complete tumor necrosis in large lesions, the addition of transarterial chemoembolization (TACE) to RFA was proposed as means to improve treatment response. TACE involves injecting a chemotherapeutic agent into the arterial branches feeding the tumor followed by selective embolization of these vessels. The combination therapy offers several potential advantages over RFA alone including a larger ablation zone secondary to reduced heat loss following embolization, more precise assessment of tumor margins, and better control of satellite lesions. A meta-analysis of seven randomized clinical trials demonstrated improved overall survival at three years with combination RFA and TACE compared to RFA alone [odds ratio (OR) =2.27; 95% CI: 1.57–3.27] without an increase in major complications (OR =1.26; 95% CI: 0.33–4.77) (22). When examined according to tumor size, the overall survival benefit following combination therapy was evident in patients with HCC nodules larger than 3 cm, but there was no difference in survival for patients with lesions smaller than 3 cm (22). Improved survival with RFA and TACE did not demonstrate a survival benefit over liver resection, however. Both 5-year overall survival and 5-year recurrence-free survival were worse following TACE and RFA compared to liver resection in a recent randomized clinical trial (OS: 46% *vs.* 62%, P 0.01; RFS: 36% *vs.* 48%, P=0.03) (23). In addition, multiple retrospective studies showed equivalent overall survival between the two treatments for HCC lesions smaller than 5 cm; recurrence-free survival was either equivalent or better following resection in these studies (24-27).

Microwave ablation, an alternative ablation system, is a heat-based ablation technique that generates higher intra-tumoral temperatures more rapidly compared RFA systems. Microwave ablation is less susceptible to heat sink effects secondary to tumor abutment of large vessels and produces larger ablation areas compared to RFA (28). The evidence to date indicates that microwave ablation is at least equivalent to RFA for the treatment of very early and early stage HCC, but there is a paucity of studies with direct comparison between the two ablative technologies (29-31).

Although head-to-head comparisons between ablation and liver resection for the treatment of very early and early stage HCC do not strongly favor one technique over the other, the probability that a patient is truly eligible for both treatments is unlikely in clinical practice. For instance, liver resection is generally contraindicated in patients with portal hypertension, elevated bilirubin, severe comorbidities or advanced age, as well as in cases where a prohibitively extensive parenchymal resection would be required due to a small functional liver remnant. On other hand, ablation of subcapsular tumors or tumors near the gallbladder, the diaphragm or vital vessels/biliary branches confers a high risk to the patient. Accordingly, the selection of treatment, liver resection or ablation, is more often driven by factors beyond those addressed in comparative studies (32).

Orthotopic liver transplant is the treatment of choice for patients with HCC. Liver transplantation removes

the tumor and eliminates the liver dysfunction as well as the predisposition to tumor recurrence. Comparative evaluations from observational studies between liver transplant and other treatment modalities for HCC have consistently demonstrated better outcomes following liver transplant. In a meta-analysis of 62 studies, liver transplant was associated with improved overall survival (OR =1.77; 95% CI: 1.45–2.16), and recurrence-free survival (OR =5.58; 95% CI: 4.12–7.55), as well as lower recurrence (OR =0.2; 95% CI: 0.15–0.28) compared to liver resection (33). In patients with early stage HCC and Child-Pugh class A cirrhosis, overall survival was comparable between both liver transplant and resection, albeit the recurrence rate remained higher following liver resection. In this subset group, liver resection is possibly more cost-effective than liver transplant (34).

Liver transplants can be deceased donor or living donor transplants. In the United States and Europe, deceased donor liver transplants (DDLT) are performed routinely, whereas over 90% of liver transplants in Asia are living donor liver transplants (LDLT) (35). In a meta-analysis that included 633 LDLT and 1232 DDLT accrued from 12 observational studies, recurrence-free survival was worse in LDLT compared to DDLT (HR =1.59; 95% CI: 1.02–2.49), but overall survival was comparable (HR =0.97; 95% CI: 0.73–1.27) (36).

The main limitation of liver transplant is shortage of organ donors. Thus, liver transplant has been prioritized to patients expected to gain the most benefit from the procedure. At present, most treating institutions adopted the Milan criteria for allocation of cadaveric livers for transplantation. Patients within the Milan criteria and eligible for donor allocation meet the following criteria: one tumor less than 5 cm or up to three nodules less than 3 cm each without extrahepatic metastasis or macrovascular tumor invasion (37). Five-year overall survival following liver transplant for patients within Milan criteria exceeds 65% which approximates the survival of patients undergoing liver transplant for non-tumor indications (38). It is this comparability in overall survival following liver transplant between HCC patients within Milan criteria and patients without cancer that prompted rapid adoption of Milan criteria and justified donor liver allocation to HCC patients.

The Milan criteria were first described more than two decades ago and have remained the standard criteria for cadaveric liver allocation. Several groups, however, have argued that the criteria are too restrictive and may exclude patients, which would have otherwise benefited from transplantation. The group at the University of California San Francisco (UCSF) proposed expanding the Milan criteria to include one nodule smaller than 6.5 cm or as many as 3 nodules smaller than 4.5 cm and a total tumor diameter size up to 8 cm (39). Several other expansion criteria proposals have been described, none however has been accepted as standard criteria in lieu of Milan for selecting liver transplant candidates with HCC (40). The increased likelihood of underestimating tumor size for lesions beyond Milan criteria (41,42), the large overlap with Milan criteria leading to only modest increase in eligible patients (5% to 10% increase with the UCSF criteria) (43), and the need for prospective validation studies with large enough sample sizes to compare outcomes of patients within Milan criteria to those beyond Milan criteria constitute some of several reasons that have hampered adoption of expanded criteria for liver transplant (40,44).

Basing transplant selection criteria on tumor size and number of nodules highlights the importance of these factors in predicting tumor recurrence post-transplant and patient survival. Following liver transplantation, overall survival can be predicted according to a predictive survival model developed by the Metroticket Investigator Study Group which incorporates different combinations of tumor size and nodule number, as well as the presence or absence of microvascular invasion (45). Large tumor size and increased nodule number are associated with increased risk of microvascular invasion, poor differentiation, and microsatellite lesions, all of which are surrogates to tumor aggressiveness (38). It has been argued, however, that tumor size and number of lesions display a one-time static snapshot of a patient's tumor. "Dynamic" tumor characteristic may reflect tumor biology better and potentially predict recurrence more accurately. Accordingly, tumor response to TACE and progression of alfa-fetoprotein (AFP) levels over time have been proposed to supplement tumor size and nodule number. Complete response, as well as partial response, following TACE were associated with improved survival post-transplant compared to patients that did not response to TACE (46,47). Also, an increase of pre-transplant AFP level beyond 15 ng/mL per month predicted worse 5-year survival compared to patients in whom AFP progression was absent or less than 15 ng/mL/month (48). Future studies validating the predictive power of responsiveness to TACE and AFP progression may motivate incorporating these markers into the selection criteria in HCC patients for liver transplant.

Tumor downstaging to meet Milan criteria is an ancillary

method used to maximize the number of patients with HCC to receive a liver transplant. Locoregional therapies including transarterial chemoembolization (TACE) are most commonly used in downstaging treatment. Other treatment modalities including ablation, resection, and radioembolization have been employed as well (40). Following successful downstaging therapy to within the Milan or institutionally adopted criteria, patients typically wait time 3 to 6 months prior to undergoing transplantation (49). The wait time has been adopted recently as means to exclude patients with aggressive tumor biology. In a meta-analysis of 13 studies, nearly half of patients initiated on downstaging therapy were successfully downstaged to within Milan criteria (50). Overall survival post-transplant was widely variable across studies, and recurrence was 16%, which is considerably higher compared to patients originally within Milan criteria (less than 5%) (45,50). At present, downstaging is unlikely to receive robust endorsement due to inconsistent entry criteria, lack of validation studies, as well as heterogeneity in downstaging protocols and outcomes assessment standards.

BCLC B

Patients with BCLC B, or intermediate stage HCC, have a large tumor burden not amenable to curative treatment, but no evidence of spread extrahepatically or within major vascular structures. These patients also have preserved liver function and limited cancer-related symptoms impacting performance status. Locoregional therapies including TACE and transarterial radioembolization remain the mainstay of treatment for BCLC B patients.

The treatment of HCC with TACE has been largely driven by two randomized clinical trials that demonstrated improved overall survival following TACE (compared to supportive care) in patients that are not amenable to curative options (51,52). In the first trial, Lo *et al.* demonstrated a survival benefit in patients randomized to TACE using an emulsion of cisplatin mixed in Lipiodol and gelatin sponge embolic particles compared to patients randomized to best supportive care (HR =0.50; 95% CI: 0.3–0.81) (52). In the second trial, Llovet *et al.* reported improved survival in patients undergoing TACE using a doxorubicin-Lipiodol emulsion with gelatin sponge embolic particles compared to supportive care (HR =0.47; 95% CI: 0.25–0.91) (51).

The trial findings reported by Lo *et al.* and Llovet *et al.* have been challenged by a Cochrane review which concluded there is not enough evidence to support TACE for patients with unresectable HCC (53). The discrepancy in the results underscores the large variability in TACE administration protocols among institutions, the number of TACE treatments administered, and the timing of follow-up imaging. Nevertheless, TACE has been adopted as the standard of care for the treatment of intermediate stage HCC at most institutions, and it is unlikely that any further clinical trials comparing TACE to supportive care would be pursued.

TACE is a catheter-based intra-arterial procedure that exploits the predominant hepatic arterial supply to HCC lesions. In a conventional TACE procedure, a chemotherapeutic agent, usually doxorubicin or cisplatin mixed with Lipiodol which increases exposure of the tumor to the drug, is delivered into the hepatic arterial branches supplying the HCC lesion, then followed by selective embolization of these branches with embolic particles (54). The resultant cytotoxicity and tissue ischemia induce tumor necrosis. A more recently introduced Lipiodol-free delivery system that uses doxorubicin loaded drug-eluting beads, DEB-TACE, delivering chemotherapy to the tumor in a more controlled and sustained fashion. Compared to conventional TACE, DEB-TACE is better tolerated largely due to lower systemic concentrations of doxorubicin. There has been no difference, however, in response rates or tumor progression and survival between conventional TACE and DEB-TACE according to two randomized controlled trials (55,56).

Not all patients with intermediate stage HCC benefit equally from TACE. Optimal candidates are patients with solitary or limited multifocal disease and relatively well-preserved liver function (9,57). In those, the median survival following TACE may be as high as 40 months and serious complications such as post-embolization syndrome (abdominal pain, fever, and nausea) and liver failure occur in less than 5 percent of cases (58). On the other hand, patients with extensive disease (>10 cm), poor residual liver function, impaired portal blood flow, and/or untreated high-risk varices are likely to suffer serious adverse events such that TACE becomes contraindicated (9,57).

Effective treatment of HCC typically necessitates delivering more than one cycle of TACE (59). Multiple treatments may be given either at fixed time intervals, also known as scheduled TACE, or on-demand according to treatment response after each TACE cycle. It is clear, however, that an aggressive TACE schedule increases the incidence of complications (60,61). Treatment of TACE is usually repeated unless no substantial tumor response

is demonstrated after two cycles of TACE, significant progression ensues including vascular invasion, extrahepatic spread, or untreatable growth/new lesion, or deterioration in liver function or performance status renders retreatment unsafe (62). The decision to discontinue TACE could be further guided by scoring systems, such as the Assessment for Retreatment with TACE (ART) score, which incorporates radiologic response, Child-Pugh score, and AST level to identify patients that are less likely to benefit from additional TACE procedures (63).

Radioembolization, or TARE, is another locoregional treatment option for patients with intermediate stage HCC. In this procedure, microspheres carrying yttrium-90 (^{90}Y), a high-energy radiation emitter with a short half-life (2.7 days) and shallow tissue penetrance, are injected selectively into the arterial branches supplying the HCC lesion. The anti-tumoral effects are mediated by microembolization of the tumor microvasculature with high-energy radiation emission (64).

TARE is equally efficacious to TACE in patients with intermediate stage HCC according to several observational studies. In a retrospective review of 103 patients with BCLC B, tumor response by EASL criteria was similar following TARE and TACE (71% *vs.* 66%, P=0.66) (65). Time-to-progression was longer following TARE (13.3 months *vs.* 9.4 months, P=0.05); however, this benefit did not translate to improvement in overall survival (median survival: 17.2 *vs.* 17.5 months, P=0.42). Another retrospective review that compared TARE and TACE demonstrated a slight advantage in overall survival following TARE in patients without portal vein thrombus or extrahepatic metastasis (median survival: 16 months *vs.* 12 months, P<0.05) (66). To date, there has not been any randomized prospective head-to-head comparisons between both treatments, and it is unlikely that there would be any, given the prohibitive sample sizes required to adequately power such a study (67).

Beyond treatment efficacy, there are several advantages to treatment with TARE compared to TACE. TARE is generally performed in an outpatient setting, whereas TACE requires hospitalization (65,66). Unlike TACE, repeated treatment with TARE is seldom needed to achieve response. In addition, TARE is typically better tolerated. The most common side effect following TARE is transient fatigue, whereas serious adverse events (grade 3 and 4 toxicities) occur in less that 5% of cases. On the other hand, abdominal pain, nausea, emesis, and fever—the post-embolization syndrome—are more common after TACE. Finally, TARE, unlike TACE, can be performed in patients with portal vein thrombosis.

TARE, however, is costlier than TACE. Based on Medicare reimbursement in the United States, one TACE session including an overnight hospitalization costs $17,000; in contrast, TARE costs $31,000 ($48,000 in case an intervention is performed in both liver lobes) (68). Nevertheless, the cost-effectiveness of TARE in comparison to TACE as the standard of care for BCLC B patients is yet to be defined. Additional costs incurred secondary to repeated treatment cycles and hospitalization for complications as well as valid outcome estimates have not been properly addressed in previously published cost-effectiveness studies.

BCLC C

BCLC C, or advanced stage HCC, comprises patients with tumor extension into the hepatic vasculature, usually the portal or hepatic veins, patients with spread beyond the liver (including extrahepatic nodal metastasis), and/or patients with cancer-related symptoms (performance status 1 or 2). This classification emanated from the landmark BCLC study in 1999, which showed portal invasion, metastasis, and constitutional symptoms (or performance status) were independent predictors of worse prognosis in patients with unresectable HCC and preserved liver function (69). Within the BCLC C group, there remains marked variability in patient prognosis and several recent studies concluded that further stratification by vascular invasion and distant spread is warranted (70,71).

The standard of care for patients with advanced stage HCC, at present, is treatment with the systemic agent, sorafenib. Sorafenib, an oral multikinase inhibitor with effects on cell proliferation, angiogenesis, and cell apoptosis (72), was approved for the treatment of advanced HCC in 2008 after demonstrating a survival benefit compared to supportive care in two landmark phase III randomized clinical trials: the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and the Asia-Pacific trial. In the SHARP trial, a total of 602 patients with advanced stage HCC accrued from over 120 centers in Europe, the Americas, and Australia were randomized to receive sorafenib or placebo. There was a longer time to radiologic progression in the sorafenib group (5.5 *vs.* 2.9 months, P<0.01) and nearly a 3-month improvement in overall survival compared to placebo (median overall survival: 7.9 *vs.* 10.7 months, P<0.01) (73). The companion Asia-Pacific randomized controlled phase III trial demonstrated the efficacy of sorafenib in

Table 1 Completed first and second line phase III clinical trials in advanced stage HCC

Author	Year	Drug	Median overall survival (months)	Hazard ratio* (P value)
First line				
Llovet (73)	2008	Placebo	7.9	0.69 (<0.01)
		Sorafenib	10.7	
Cheng (74)	2009	Placebo	4.2	0.68 (0.01)
		Sorafenib	6.5	
Johnson (77)	2013	Sorafenib	9.9	1.06 (0.31)
		Brivanib	9.5	
Cheng (78)	2013	Sorafenib	10.2	1.30 (< 0.01)
		Sunitinib	7.9	
Cainap (79)	2015	Sorafenib	9.8	1.05 (0.52)
		Linifanib	9.1	
Zhu (80)	2015	Sorafenib	8.5	0.92 (0.20)
		Sorafenib and Erlotinib	9.5	
Second line				
Llovet (81)	2013	Placebo	8.2	0.89 (0.30)
		Brivanib	9.4	
Zhu (82)	2014	Placebo	7.3	1.05 (0.68)
		Everolimus	7.6	
Zhu (83)	2015	Placebo	7.6	0.86 (0.13)
		Ramucirumab	9.2	
Abou-Alfa (84)	2016	Placebo	7.4	1.02 (0.88)
		ADI-peg 20	7.8	
Bruix (85)	2016	Placebo	7.8	0.63 (<0.01)
		Regorafenib	10.6	

*, first drug in each trial is reference.

a predominantly Asian cohort of HCC patients. Similar findings to the SHARP trial were shown including doubling of the time to progression (2.8 *vs.* 1.4 months, P<0.01) and over a 2-month improvement in overall survival (6.5 months *vs.* 4.2 months, P<0.01) in the sorafenib group (74).

The addition of sorafenib to the treatment of HCC represents a breakthrough in the management of patients with advanced HCC who were, until 2008, offered predominantly supportive care. Sorafenib, however, has several limitations. First, sorafenib is poorly tolerated such that 20 to 38 percent of patients discontinue the drug due to drug-related adverse events (73,74). The most common serious side effects (toxicity grades 3 and 4) are hand-foot skin reaction and diarrhea. Interestingly, having adverse events correlates with better outcome (75). Second, primary resistance is a significant issue which has reflected in disease control rates are rarely exceeding 50% (73,74). Secondary resistance usually develops after several weeks of therapy initiation, which may explain the short time to progression intervals in the SHARP and Asia-Pacific trials. Last, there is very little evidence that sorafenib impacts survival in patients with Child-Pugh classes B and C (76).

Following sorafenib, several agents have been evaluated in phase III trials for the treatment of HCC (*Table 1*).

Table 2 Ongoing patient enriched clinical trials in HCC

Clinicaltrials.gov identifier	Phase	Intervention arms	Target patient group
NCT02029157	III	Tivantinib *vs.* Placebo	High MET
NCT02435433	III	Ramucirumab *vs.* Placebo	AFP >400 ng/mL
NCT01507168	II	RO5137382 *vs.* Placebo	Glypican-3 expression
NCT01915602	II	Refametinib *vs.* Sorefenib	KRAS or NRAS mutations
NCT02115373	I/II	MSC2156119J	High MET
NCT02508467	I	BLU-554	Aberrant FGF19/FGFR4 pathway

Table 3 Ongoing clinical trials involving immune checkpoint inhibitors in HCC

Drug	Target	Clinicaltrials.gov identifier
Nivolumab	PD-1	NCT02576509, NCT01658878, NCT02859324
Pembrolizumab	PD-1	NCT02702401, NCT02702414
Durvalumab	PD-1	NCT02519348, NCT02821754
Tremelimumab	CTLA-4	NCT02519348, NCT02821754, NCT01853618
Ipilimumab	CTLA-4	NCT01658878

In the first-line setting, none of the trials completed to date demonstrated a survival benefit (or non-inferiority) to sorafenib for advanced stage HCC (77-80). Similarly, multiple agents proved non-efficacious in comparison to placebo in second-line trials (81-84). Failure of these trials has been attributed to various reasons including suboptimal evaluation of drug-induced liver toxicity, poor phase II study design, questionable value of time to progression and objective response rate as surrogate endpoints for survival, and absence of biomarker analysis (86,87). The latter reason is particularly important as the overwhelming majority of trials failed to acquire tumor tissue, and as a result, an evaluation of drug efficacy in molecularly selected patient subgroups was not possible.

Recently a second line treatment of advanced HCC in patients failing first line sorafenib therapy was reported. The Study of Regorafenib After Sorafenib in Patients with Hepatocellular Carcinoma (RESORCE) trial demonstrated that regorafenib, an oral multikinase inhibitor with a similar target profile to sorafenib, was shown to extend survival compared to placebo (median survival: 10.6 months *vs.* 7.8 months, P<0.01) in patients with intermediate and advanced HCC that progressed on first-line sorafenib (85). With these findings, regorafenib would be the only second-line agent for the treatment of HCC to demonstrate efficacy.

The search for agents more effective and better tolerated than sorafenib for the treatment of advanced HCC continues to be very active. The majority of ongoing clinical trials investigating these agents can be broadly classified into two types: patient enrichment trials and immune checkpoint inhibitor trials. *Table 2* details several open patient enrichment trials. For instance, the JET-HCC trial (NCT02029157) is a phase III trial evaluating tivantinib for second-line treatment of advanced stage HCC in patients with MET-high tumors. It follows a placebo-controlled phase II trial in which the subset of patients with MET-high tumors demonstrated improved overall survival after treatment with tivantinib (88). Similarly, ramucirumab is being investigated in HCC patients with elevated AFP (400 ng/mL) following favorable outcomes in a subgroup of patients with increased levels of AFP levels in a trial of ramucirumab as a second-line therapy (83). The second type of trials in advanced stage HCC concerns immune check-point inhibitors such as inhibitors of PD-1 and CTLA-4. In early phase trials, nivolumab, a PD-1 inhibitor, and tremelimumab, a CTLA-4 inhibitor, showed promising response rates in patients with advanced HCC (89,90). Confirmatory phase III trials are currently underway (*Table 3*).

BCLC D

HCC patients with poor liver function (Child-Pugh class C) and/or prohibitive ECOG performance status (PS >2) are classified BCLC D, or terminal stage HCC, irrespective of tumor burden. The prognosis of this patient group is weeks to few months, and they are managed with best supportive care. Notably, BCLC D patients secondary to impaired liver

function in whom HCC is within transplant criteria may be considered for liver transplant.

Conclusions

In conclusion, HCC is a significant and increasing cause of cancer burden globally and in the western world. Patient prognosis remains dismal and novel treatment options, particularly for patients with advanced HCC, are lagging owing to our poor understanding of the molecular drivers of HCC. At present, this is an active area of research that holds promise to uncover implicating carcinogenic pathways and identify actionable genetic and molecular aberrations that can be translated into targeted therapies.

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Footnote

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