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Therapies for Advanced Stage Hepatocellular Carcinoma With Macrovascular Invasion or Metastatic Disease: A Systematic Review and Meta-analysis

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Hepatocellular carcinoma (HCC) is a complex disease most commonly arising in the background of chronic liver disease. In the past two decades, there has been a significant increase in our understanding of both the clinical and molecular heterogeneity of HCC. There has been a robust increase in clinical trial activity in patients with poor prognostic factors, such as macrovascular invasion and extrahepatic spread (EHS). We aimed to synthesize the evidence for the treatment of patients with advanced HCC based on these baseline characteristics, including patients with both Child-Pugh (CP) scores of A and B. A comprehensive search of several databases from each database inception to February 15, 2016 any language was conducted. We included 14 studies (three randomized controlled studies [RCTs] and 11 observational studies). We included studies that compared sorafenib, transarterial bland embolization/transarterial chemoembolization, yttrium-90/radiation therapy, ablation (or combination), and no therapy. Two RCTs comparing sorafenib to best supportive care demonstrated a consistent improvement in overall survival (OS) for patients with advanced HCC and metastatic vascular invasion (MVI) and/or EHS and CP A liver disease (hazard ratio, 0.66 [95% confidence interval, 0.51-0.87]; $I^2 = 0\%$). Several observational studies evaluated locoregional therapies alone or in combination with other treatments and were limited by very-low-quality of evidence. This was true for both patients with EHS and MVI. *Conclusion*: In patients with advanced HCC and CP A liver function, sorafenib is the only treatment that has been shown to improve OS in randomized studies. High-quality data supporting the use of other treatment modalities in this setting, or in the setting of patients with less compensated (CP B) liver disease, are lacking. (HEPATOLOGY 2018;67:422-435)

The optimal management of hepatocellular carcinoma (HCC) requires a multidisciplinary approach that brings together expertise in liver surgery, hepatology, interventional radiology, and medical oncology. Current recommendations for screening aim to identify smaller tumors that can be treated with curative intent with surgical resection, radiofrequency ablation (RFA), and/or liver transplant.[1] However, a large number of patients present with disease beyond criteria that would be considered for curative approaches.

Historically there has been a large unmet need for systemic treatments in HCC. Only in 2008 were data with the multikinase inhibitor, sorafenib, shown to

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; CI, confidence interval; CP, Child-Pugh; cryoRx, cryotherapy; EHS, extrahepatic spread; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HR, hazard ratio; MVI, metastatic vascular invasion; OR, odds ratio; OS, overall survival; PICO, population, intervention, comparison, and outcomes; PVE, portal vein embolization; PVTT, portal vein tumor thrombosis; RCTs, randomized controlled studies; RFA, radiofrequency ablation; RR, risk ratio; RT, radiation therapy (external beam); TABE, transarterial bland embolization; TACE, transarterial chemoembolization; TAE, transarterial embolization; Y90, yttrium-90.

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improve survival greater than placebo.[2] Since that time, despite numerous attempts to improve upon these results, no study has demonstrated a survival benefit over sorafenib alone in a randomized study.[3]

The unique dual blood supply to the liver, dependence of HCC on an arterial blood supply, and hypervascular nature of HCC have made it an attractive target for catheter-based locoregional therapies. Although there is no standardized technique for transarterial chemoembolization (TACE) or universal application in terms of number and frequency, the procedure generally involves the selective catheterization of tumor feeding arterial vessels with the subsequent infusion of cytotoxic agents followed by embolizing the vessels. The definitive randomized controlled studies and meta-analyses that have established a role for TACE in HCC were selective in terms of tumor size and characteristics excluding patients with metastatic vascular invasion (MVI) and/or extrahepatic spread (EHS).[4,5] Since that time, there has been broad application of locoregional therapies in practice often beyond the criteria of those used in clinical studies. Radioembolization is a newer technique that is a catheter-based approach of delivering radiolabeled (yttrium-90; Y90) beads into the tumor bed.[6] Studies with locoregional therapies such as TACE and radioembolization with Y90 have been performed to establish the efficacy and safety of these approaches in patients with MVI.

We conducted this systematic review and meta-analysis to synthesize existing evidence about effectiveness of systemic and locoregional approaches to treating advanced HCC with MVI or EHS.

Materials and Methods

We followed a predefined protocol developed by HCC guideline and systematic review writing committees of the American Association of for Liver Disease (AASLD). We reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7]

ELIGIBILITY CRITERIA

We included comparative studies that enrolled adults with Child-Pugh (CP) grade A or B cirrhosis and advanced stage HCC with macrovascular invasion and/or metastatic disease. We included studies that compared sorafenib, transarterial bland embolization (TABE)/TACE, Y90/radiation therapy, ablation (or combination), and no therapy. Outcome of interest was mortality or survival. We excluded studies that included CP grade C cirrhosis, studies with advanced HCC but did not report separate outcomes for macrovascular invasion and/or metastatic disease, noncomparative studies, no mortality or survival outcomes reported, case reports, cohorts with less than 5 patients, reviews, letters, errata, commentaries, and studies published only as abstracts. Table 1 describes the population, intervention, comparison, and outcomes (PICO) criteria of the two questions of interest.

SEARCH STRATEGY

A comprehensive search of several databases from each database inception to February 15, 2016 any

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TABLE 1. PICO of the Proposed Questions

	Q1	Q2
Population	Adults with CP class A or B cirrhosis and advanced-stage HCC with macrovascular involvement	Adults with CP class A or B cirrhosis and advanced-stage HCC with metastatic disease
Intervention vs. comparison	Sorafenib versus TABE/TACE/Y90/RT vs. ablation (or combination) vs. no therapy	Sorafenib versus TABE/TACE/Y90/RT vs. ablation (or combination) vs. no therapy
Outcomes	Mortality	Mortality
Study design	Comparative studies	Comparative studies

language was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from investigators. Supporting Table S1 shows the detailed search strategy.

STUDY SELECTION

Using an online reference management system (DistillerSR; Evidence Partners, Inc., Ottawa, Ontario, Canada), two reviewers were independently screened the titles and abstracts for potential eligibility. Full-text versions of the included abstracts were retrieved and screened in duplicate. Disagreements were harmonized by consensus and, if not possible by consensus, through arbitration by a third reviewer.

DATA EXTRACTION

We extracted the following variables from each study: study characteristics, including primary author and time period of study/year of publication; patient baseline characteristics, including number of patients, age, number of lesions, size of hepatic lesions, level of alpha-fetoprotein (AFP), stage of HCC, CP score, and cause of cirrhosis; previous treatment; intervention details; and outcomes of interest.

METHODOLOGICAL QUALITY AND RISK OF BIAS ASSESSMENT

We used a Cochrane risk of bias tools to assess the methodological quality of randomized controlled studies (RCTs) and modified Newcastle-Ottawa Scale to assess the methodological quality of observational studies. Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8] We used the following criteria to evaluate quality of evidence: risk of bias; indirectness (i.e., surrogate outcomes); imprecision (i.e., wide confidence intervals [CIs]); inconsistency or heterogeneity; and publication bias.

STATISTICAL ANALYSIS

We extracted hazard ratios (HRs) with 95% CIs and calculated risk ratios (RRs), and 95% CI using bimanual distribution. We then pooled the log-transformed HRs/RRs using the fixed-effect model because of the small number of included studies. I^2 was used to assess heterogeneity, with values over 50% suggesting high heterogeneity. Statistical analyses were conducted using Stata software (version 13; StataCorp LP, College Station, TX). Because of the small number of studies, we could not assess publication bias by examining funnel plot asymmetry or Egger's regression test.

Results

The initial search resulted in 2,779 citations for both questions. We eventually included 14 studies (three RCTs[2,9,10] and 11 observational studies[11-21]). Figure 1 shows the study selection process. Detailed baseline characteristics of the studies are described in Table 2.

METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES

For RCTs (Fig. 2), all the studies reported complete outcome data and no selective reporting. Two studies reported random sequence generation and blinding of the participants and personnel. One study reported blinding of the outcome assessment, and no studies reported allocation concealment. For observational studies (Fig. 3), the overall risk of bias is high attributed to unclear or high risk of bias in selection of cohorts, outcome assessment, adequacy of follow-up,

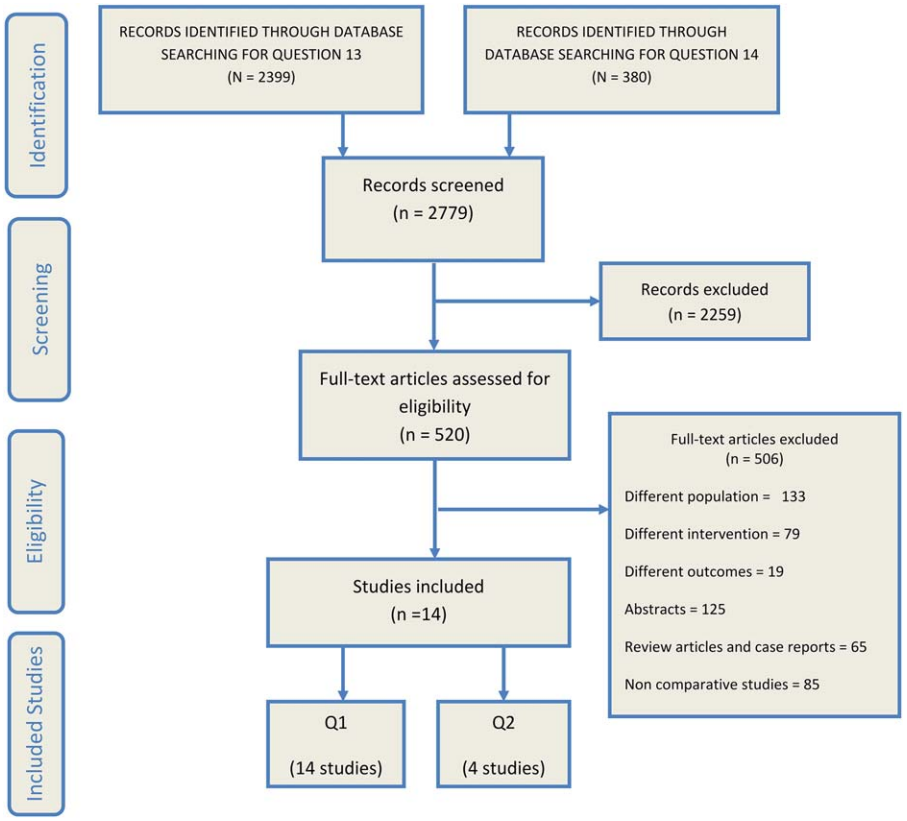

FIG. 1. The process of study selection.

and lack of source of funding reporting. Assessment of the methodological quality for the studies included is reported in Tables 3 and 4.

Q1: INTERVENTIONS TO TREAT ADULTS WITH CHILD CLASS A OR B CIRRHOSIS AND ADVANCED STAGE HCC WITH MACROVASCULAR INVASION

Fourteen comparative studies compared several interventions to treat adults with CP class A or B cirrhosis and advanced HCC with macrovascular involvement. Eleven studies[9,11,13-21] included advanced HCC patients with portal vein tumor thrombosis (PVTT). Summary of the evidence is presented in Table 5.

Two RCTs[2,10] compared sorafenib versus placebo and reported overall survival (OS) as outcome of interest. The majority of patients enrolled in the two studies were CP class A cirrhosis (96.6%). Compared to placebo, sorafenib improved OS with moderate quality of evidence (HR, 0.66 [95% CI, 0.51-0.87]; $I^2 = 0\%$).

One RCT[9] compared sorafenib plus cryotherapy (cryoRx) versus sorafenib alone and enrolled 104 HCC patients. A total of 80.9% of the patients were CP class A cirrhosis. Compared to sorafenib alone, sorafenib plus cryoRx showed no statistical significant improvement in 1-year survival rate with moderate quality of evidence (RR, 1.7 [95% CI, 0.99-2.78]).

One observational study[19] compared percutaneous RFA versus control. The study enrolled 57 advanced HCC patients with PVTT. A total of 78.9% of patients were CP class A cirrhosis. Compared to control, percutaneous RFA reduced mortality (RR, 0.81 [95% CI, 0.67-0.97]). Quality of evidence was very low downgraded attributed to imprecision and serious risk of bias.

One observational study[20] compared TACE versus radioembolization (Y90) and enrolled 323 advanced

TABLE 2. Characteristics of the Included Studies

Author, Year	Study Design/ Country	Intervention	Patients (n)	Male (n)	Age (Years)	Staging	Lesions (n)	CP Score	Size of the Nodules (cm)	AFP (ng/mL)	Follow-up (Months)	Etiology of HCC	Previous Treatment
Akiyama, 2008[21]	Cohort/ Japan	Hepatic arterial infusion with a low dose of CDDP and 5-FU administered over a 6-hour period on days 1-5 of the first and second week	10	8	56.1 ± 15.7	TNM = 3.7 ± 0.48	NR	7.0 ± 2.10	NR	>7 = 7	NR	HBV: 4 HCV: 5 No HBV HCV: 1	NR
		Supportive care	13	11	67.1 ± 9.7	TNM = 3.8 ± 0.37	NR	8.5 ± 2.20	NR	>7 = 10	NR	HBV: 4 HCV: 8 No HBV HCV: 1	NR
Carr, 2010[20]	Cohort/ North America	TACE: 125 mg/m^2 of body surface area of cisplatin in 1 mg/mL of normal saline and infused into the right or left hepatic artery	691	518	NR	NR	1:518	NR	NR	465	NR	Alcohol: 217 HBV: 97 HCV: 132	NR
		Y90: 135-150 Gy to the treated lobe with bolus injection over 1-5 minutes into the right or left hepatic artery	99	70	NR	NR	1:70	NR	NR	58	NR	Alcohol: 37 HBV: 9 HCV: 30	
Cheng, 2009[10]	RCT/China, Taiwan, South Korea	Sorafenib: 400 mg orally twice-daily for 6 weeks	150	127	51 (23-86)	BCLC C: 143	1:20 2:52 3:30 ≥4:48	A: 74 B: 2	NR	116 ± 77.3	20	NR	NR
		Placebo	76	66	52 (25-79)	BCLC C: 73	1:5 2:27 3:14 ≥4:30	A: 146 B: 5	NR	59 ± 77.6	20	NR	
Giorgio, 2014[19]	Case control/ USA, Italy	Percutaneous RFA: of both the intrahepatic nodules and the portal thrombus under general anesthesia	35	22	71 ± 5	NR	1:35	A: 28 B: 7	3.7 ± 5.0	78.84 ± 91.61	8-60	HBV: 7 HCV: 28	NR
		Controls: untreated patients	22	15	73 ± 3	NR	1:22	A: 17 B: 5	4.3 ± 0.4	78.46 ± 1.00	2-10	HBV: 5 HCV: 17	
Kim, 2015[18]	Retrospective study/Korea	Chemoembolization: TACE	295	258	53 (46-60)	NR	NR	A: 245 B: 50	NR	≥400: 204 ≥20: 256	8	HBV: 230 HCV: 28 HBV and HCV: 8 Other: 29	Sorafenib treatment for at least 4 weeks
		Chemoembolization/RT: TACE followed by RT to target PVTT 2-3 weeks after the first chemoembolization session	196	173	52 (46-60)	NR	NR	A: 125 B: 71	NR	≥400: 109 ≥20: 157	10.4	HBV: 175 HCV: 7 HBV and HCV: 1 Other: 13	
		Sorafenib: 400 mg orally twice-daily	66	54	52 (46-59)	NR	NR	A: 43 B: 23	NR	≥400: 43 ≥20: 59	4	HBV: 57 HCV: 3 HBV and HCV: 0 Other: 6	
Llovet, 2008[2]	RCT/Europe, Australasia, North America, Central and South America	Sorafenib: 400 mg orally twice-daily	299	260	64.9 ± 11.2	BCLC B: 54 BCLC C: 244	NR	A: 284 B: 14	NR	44.3	13	HBV: 56 HCV: 87 Alcohol: 79 Other: 28 Unknown: 49	NR

TABLE 2. *Continued*

Author, Year	Study Design/ Country	Intervention	Patients (n)	Male (n)	Age (Years)	Staging	Lesions (n)	CP Score	Size of the Nodules (cm)	AFP (ng/mL)	Follow-up (Months)	Etiology of HCC	Previous Treatment
		Placebo	303	39	66.3 ± 10.2	BCLC B: 51 BCLC C: 252	NR	A: 297 B: 6	NR	99	13	HBV: 55 HCV: 82 Alcohol: 80 Other: 29 Unknown: 56	
Marelli, 2009[17]	Retrospecti-ve study/UK	I-lipiodol (1,000 MBq)	50	44	59 ± 11	BCLC A: 22 BCLC B: 23 BCLC C: 0 BCLC D: 5	1:22 2:8 3:6 ≥4:14	A: 31 B: 14 C: 5	0.45 ± 0.3	142 (2-10,000)	5.6 (0.3-35.1)	HBV: 8 HCV: 20 Alcohol: 5 Virus + alcohol: 3 Others: 14	NR
		TAE/TACE: Embolization was performed using polyvinyl alcohol particles (Ivalon; diameter, 150-500 mm) under fluoroscopic guidance until flow was stopped.	74	63	61 ± 10	BCLC: A: 29 BCLC B: 42 BCLC C: 0 BCLC D: 3	1:36 2:18 3:5 ≥4:14	A: 43 B: 28 C: 3	0.51 ± 0.34	29 (2-10,000)	9 (0.3-56.8)	HBV: 14 HCV: 22 Alcohol: 9 Virus + alcohol: 6 Others: 23	
Nagai, 2015[16]	Retrospective study/Japan	Hepatic arterial infusion chemotherapy	20	16	66.4 ± 7.0	Stage IVA: 15 IVB: 5	NR	A: 11 B: 7	NR	54,861.6 ± 99,114.0	84	HBV: 5 HCV: 8 Other: 5	NR
		SF-HAIC group: HAIC after receiving treatment with sorafenib (400-800 mg)	18	16	69.0 ± 6.0	Stage IVA: 13 IVB: 5	NR	A: 6 B: 15	NR	15,237.9 ± 28,707.0	60	HBV: 4 HCV: 11 Other: 6	
Nakazawa, 2014[15]	Retrospective study/Japan	Sorafenib: 400 mg twice-daily or 200 mg twice-daily	28	23	70 (61-78)	NR	NR	A: 28	NR	680 (37-3,708)	NR	HCV: 16	TACE/TAI: 15 RFA: 2 RT: 1
		3D-CRT: A daily radiation dose of 1.8-2.0 Gy was administered with 6- or 10-MV x-rays using two- to four-port combinations.	28	19	67 (61-70)	NR	NR	A: 28	NR	43 (10-1,096)	NR	HCV: 17	TACE/TAI: 20
Song, 2015[14]	Retrospective/ Korea	Sorafenib	60	44	55.8 ± 9.0	NR	NR	A: 47 B: 13	<10:31 ≥10:29	<200: 20 ≥200: 38	50	HBV: 41 HCV: 5 Alcohol: 8 Others: 6	Yes: 21 No: 39
		Hepatic arterial infusion chemotherapy	50	38	54.3 ± 9.9	NR	NR	A: 45 B: 5	<10:22 ≥10:28	<200: 15 ≥200: 35	40	HBV: 44 HCV: 2 Alcohol: 3 Others: 1	Yes: 19 No: 31
Tan, 2014[13]	Retrospective study/China	Transcatheter arterial chemoembolization	64	42	56 (44-76)	NR	NR	A: 32 B: 30	7.5 (4.2-14.3)	NR	3	HBV: 41 Non-HBV: 23	NR
		Transcatheter arterial chemoembolization plus portal vein embolization	52	33	61 (45-80)	NR	NR	A: 25 B: 27	7.2 (3.2-15.1)	NR	3	HBV: 35 Non-HBV: 17	
Yang, 2012[9]	Case control/ China	Sorafenib-cryoRx: 400 mg sorafenib twice-daily for at least 8 weeks. Following sorafenib treatment, cryoRx was conducted in those without absolute contraindications.	52	48	51.2 ± 11.9	C: 52	52	A: 41 B: 11	8.39 ± 4.38	NR	10.5 (4-26)	HBV: 52	NR

TABLE 2. *Continued*

Author, Year	Study Design/ Country	Intervention	Patients (n)	Male (n)	Age (Years)	Staging	Lesions (n)	CP Score	Size of the Nodules (cm)	AFP (ng/mL)	Follow-up (Months)	Etiology of HCC	Previous Treatment
		Sorafenib (control): 400 mg sorafenib twice-daily for at least 8 weeks	52	47	52.6 ± 8.3	C: 52	52	A: 43 B: 9	8.32 ± 2.72	NR	10.5 (4-26)	HBV: 52	
Yoon, 2014[12]	Retrospective study/Korea	Sorafenibf 400 mg twice-daily	78	66	58.4 ± 10.4	BCLC B: 4 BCLC C: 74	NR	A: 60 B: 18	NR	≤200: 31 >200: 46	NR	Alcohol: 7 HBV: 52 HCV: 5 Unknown: 7 Combined: 7	Curative treatment: 3 Noncurative treatment: 40 Additive radiotherapy: 3
		Cytotoxic chemotherapy: doxorubicin 60 mg/m^2 and cisplatin 60 mg/m^2 on day 1 with capecitabine at a dose of 1,000 mg/m^2 twice-daily from day 1 through day 14	14	11	59.9 ± 11.2	BCLC B: 0 BCLC C: 14	NR	A: 10 B: 4	NR	≤200: 8 >200: 6	NR	Alcohol: 2 HBV: 9 HCV: 1 Unknown: 1 Combined: 1	Noncurative treatment: 10 Additive radiotherapy: 2
Zhang, 2015[11]	Retrospective study/China	Sorafenib-TACE: For TACE 10-20 mL of lipiodol mixed with 20-40 mg of epirubicin	45	43	50.1 ± 8.8	AJCC stage IIIA: 25 AJCC IIIB: 3 AJCC IIIC: 4 AJCC IV: 13	NR	5: 21 6: 13 7: 11	NR	<20: 3 >20: 42	7.3 (2-18)	HBV: 44	NR
		Sorafenib: oral 400 mg twice-daily	44	41	53.6 ± 9.7	AJCC stage IIIA: 20 AJCC IIIB: 4 AJCC IIIC: 6 AJCC IV: 14	NR	5: 23 6: 11 7: 10	NR	<20: 9 >20: 35	7.3 (2-18)	HBV: 42	

Abbreviations: CDDP, concomitant radiochemotherapy with cisplatin; 5-FU, 5-fluorouracil; SF, sorafenib; 3D-CRT, three-dimensional conformal radiotherapy; NR, not reported; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus.

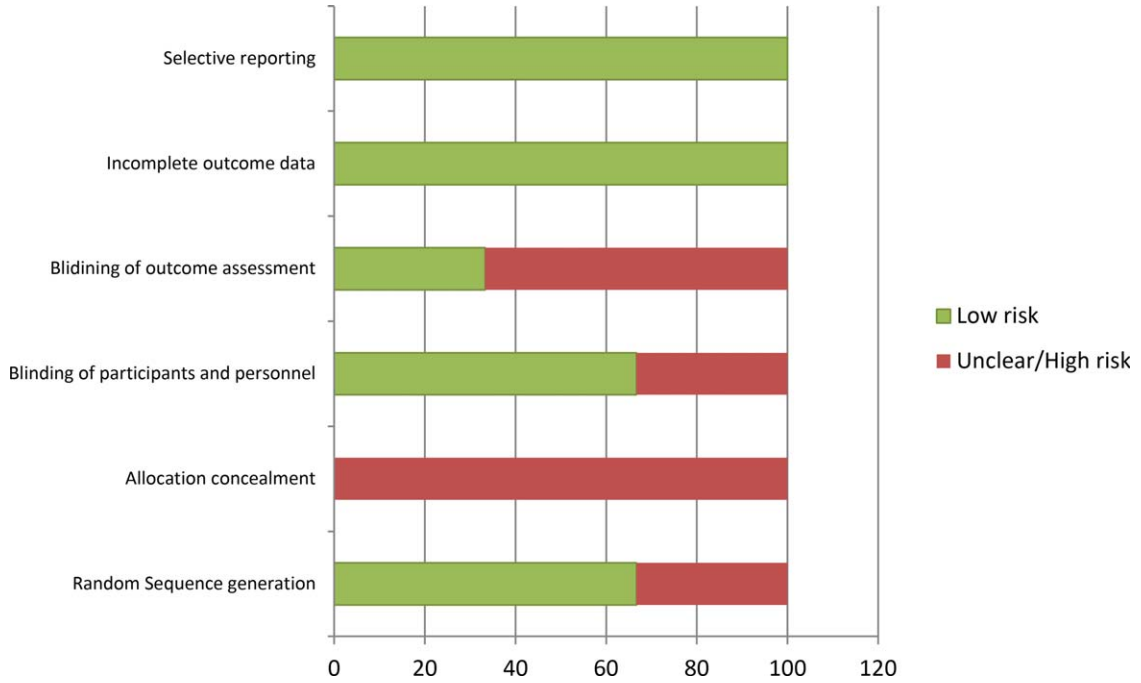

FIG. 2. Methodological quality of the RCTs.

HCC patients with PVTT. TACE improved median survival compared to Y90 with very low quality of evidence (odds ratio [OR], 2.1 [95% CI 1.04-4.2]).

One observational study[18] compared chemoembolization with/without radiation therapy (external beam; RT) versus sorafenib and enrolled advanced HCC

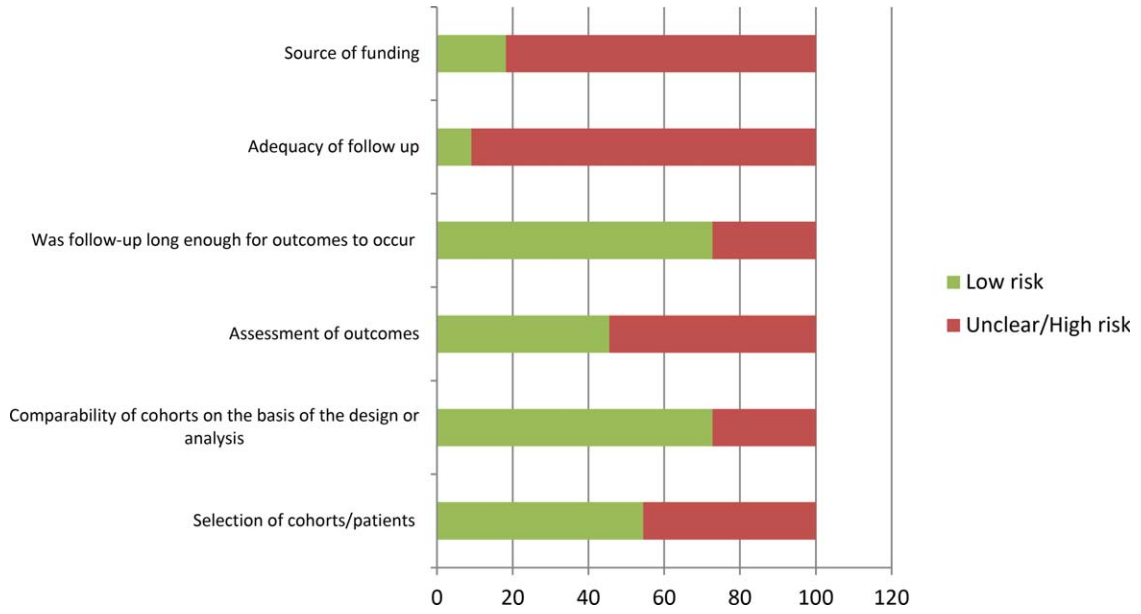

FIG. 3. Methodological quality of the observational studies.

TABLE 3. Risk of Bias Assessment of RCTs

	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome	Incomplete Outcome Data	Selective Reporting
Cheng et al., 2009	Low risk	Unclear/high risk	Low risk	Unclear/high risk	Low risk	Low risk
Llovet et al., 2008	Unclear/high risk	Unclear/high risk	Low risk	Unclear/high risk	Low risk	Low risk
Yang et al., 2012	Low risk	Unclear/high risk	Unclear/high risk	Low risk	Low risk	Low risk

patients with PVTT. In both CP class A (HR, 0.34 [95% CI, 0.24-0.48]) and CP class B (HR, 0.26 [95% CI, 0.16-0.43]) HCC patients with cirrhosis, chemoembolization with/without RT improved OS compared to sorafenib. Quality of evidence was very low downgraded attributed to imprecision and serious risk of bias.

One observational study[13] compared TACE plus portal vein embolization (PVE) versus TACE alone and enrolled 116 patients. TACE plus PVE improved 1-year survival compared to TACE alone (RR, 1.3 [95% CI, 1.05-1.7]). No significant improvement was noticed in 3- and 5-year survival rate. Quality of evidence was very low attributed to serious risk of bias and imprecision.

Several observational studies compared different intervention, including: Iodine-131-lipiodol versus TACE/transarterial embolization (TAE)[17]; cytotoxic chemotherapy versus sorafenib[12]; transhepatic arterial chemotherapy versus control[21]; hepatic arterial infusion chemotherapy (HAIC) plus sorafenib versus HAIC[16]; sorafenib versus sorafenib plus TACE[11]; radiotherapy versus sorafenib[15]; and HAIC versus sorafenib.[14] No statistical significance improvement was noticed in survival with very low quality of evidence (Table 5).

Q2: INTERVENTIONS TO TREAT ADULTS WITH CP CLASS A OR B CIRRHOSIS AND ADVANCED-STAGE HCC WITH METASTATIC DISEASE

Four studies reported enrolled CP class A or B patients with cirrhosis and advanced HCC with metastatic disease and reported mortality and /or survival outcomes. Summary of evidence is presented in Table 6.

Two RCTs[2,10] compared sorafenib versus placebo and enrolled 311 patients. CP class A cirrhosis was 96.6% of patients enrolled. Compared to placebo, sorafenib showed no statistically significant improvement of OS with moderate quality of evidence (HR, 0.84 [95% CI, 0.67-1.1]; $I^2 = 0\%$).

Two observation studies[12,18] enrolled 167 patients with advanced HCC and distant metastasis; one study compared cytotoxic chemotherapy versus sorafenib and the other compared chemoembolization with/without RT versus sorafinib. No statistically significant improvement in OS was noticed in both studies with very low quality of evidence.

TABLE 4. Risk of Bias Assessment of Observational Studies

	Selection of Cohorts/Patients or Representativeness of the Cases	Adjusting for Confounders/ Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow-up	Source of Funding Reported
Akiyama, 2008	Unclear/high risk	Low risk	Unclear/high risk	Low risk	Unclear/high risk	No
Carr, 2010	Unclear/high risk	Low risk	Unclear/high risk	Unclear/high risk	Unclear/high risk	No
Giorgio, 2014	Low risk	Low risk	Low risk	Low risk	Unclear/high risk	No
Kim, 2015	Unclear/high risk	Low risk	Unclear/high risk	Low risk	Low risk	No
Marelli, 2009	Low risk	Low risk	Low risk	Low risk	Unclear/high risk	No
Nagai, 2015	Low risk	Unclear/high risk	Low risk	Low risk	Unclear/high risk	No
Nakazawa, 2014	Unclear/high risk	Low risk	Unclear/high risk	Low risk	Unclear/high risk	No
Song, 2015	Low risk	Unclear/high risk	Unclear/high risk	Low risk	Unclear/high risk	No
Tan, 2014	Low risk	Unclear/high risk	Low risk	Unclear/high risk	Unclear/high risk	No
Yoon, 2014	Unclear/high risk	Low risk	Unclear/high risk	Unclear/high risk	Unclear/high risk	Yes
Zhang, 2015	Low risk	Low risk	Low risk	Low risk	Unclear/high risk	Yes

TABLE 5. Summary of Evidence for Outcomes Reported in Studies With Advanced HCC and Macrovascular Invasion

Intervention vs. comparison	Design	Studies (n)	Child-Pugh	Outcome	Patients (n)	ES (95% CI)	GRADE
Sorafenib vs. placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	231	HR 0.66 (0.51-0.87), $I^2 = 0\%$	⊕⊕⊕◯ MODERATE†
‡Sorafenib-cryoRx vs. sorafenib	RCT	1	Class A (80.9%) Class B (0.19%)	1-year survival rate	104	RR 1.7 (0.99-2.78)	⊕⊕⊕◯ MODERATE†
‡Percutaneous RFA vs. control	Observational study	1	Class A (78.9%) Class B (21.1%)	Mortality	57	RR 0.81 (0.67-0.97)	⊕◯◯◯ VERY LOW*,†
‡TACE vs. Y90	Observational study	1	NR	Median Survival	323	OR 2.1 (1.04-4.2)	⊕◯◯◯ VERY LOW*,†
‡131-I-lipiodol vs. TACE/TAE	Observational study	1	Class A (59.7%) Class B (33.9%) Class C (6.4%)	1-year survival rate	20	RR 2.6 (0.39-16.9)	⊕◯◯◯ VERY LOW*,†
Cytotoxic chemotherapy vs. sorafenib	Observational study	1	Class A (76.1%) Class B (23.9%)	Overall Survival	49	HR 0.5 (0.1-1.7)	⊕◯◯◯ VERY LOW*,†
‡Transhepatic arterial chemotherapy vs. control	Observational study	1	Intervention (7.0 ± 2.10) Control (8.5 ± 2.20)	6-month survival rate	23	RR 11.5 (0.69 – 190.8)	⊕◯◯◯ VERY LOW*,†
‡Chemoembolization with/without RT vs. sorafinib	Observational study	1	Class A (64.4%) Class B (35.6%)	Overall survival	262	HR 0.28 (0.20-0.40)	⊕◯◯◯ VERY LOW*,†
‡Chemoembolization with/without RT vs. sorafinib	Observational study	1	Class A (100%)	Overall survival	413	HR 0.34 (0.24-0.48)	⊕◯◯◯ VERY LOW*,†
‡Chemoembolization with /without RT vs. sorafinib	Observational study	1	Class B (100%)	Overall survival	144	HR 0.26 (0.16-0.43)	⊕◯◯◯ VERY LOW*,†
‡Chemoembolization vs. sorafenib	Observational study	1	Class A (79.8%) Class B (20.2%)	Overall survival	361	HR 0.67 (0.47-0.95)	⊕◯◯◯ VERY LOW*,†
‡Chemoembolization/RT vs. chemoembolization	Observational study	1	Class A (75.4%) Class B (24.6%)	Overall survival	491	HR 0.56 (0.45-0.71)	⊕◯◯◯ VERY LOW*,†
‡TACE + PVE vs. TACE	Observational study	1	Class A (50%) Class B (50%)	1-year survival	116	RR 1.3 (1.05-1.7)	⊕◯◯◯ VERY LOW*,†
				3-year survival rate	116	RR 1.5 (0.84-2.54)	⊕◯◯◯ VERY LOW*,†
				5-year survival rate	116	RR 15.9 (0.92-276.60)	⊕◯◯◯ VERY LOW*,†

TABLE 5. *Continued*

Intervention vs. comparison	Design	Studies (n)	Child-Pugh	Outcome	Patients (n)	ES (95% CI)	GRADE
‡HAIC + sorafenib vs. HAIC	Observational study	1	Class A (43.6%) Class B (56.4%)	1-year survival	38	RR 1.33 (0.5-3.6)	⊕◯◯◯ VERY LOW*,†
				3-year survival rate	38	RR 3.3 (0.38-29.25)	⊕◯◯◯ VERY LOW*,†
‡HAIC + sorafenib vs. HAIC	Observational study	1	Class A (100%)	1-year survival	17	RR 1.1 (0.28-4.32)	⊕◯◯◯ VERY LOW*,†
				3-year survival rate	17	RR 2.92 (0.16-52.47)	⊕◯◯◯ VERY LOW*,†
‡HAIC + sorafenib vs. HAIC	Observational study	1	Class B (100%)	1-year survival	21	RR 1.33 (0.29-6.23)	⊕◯◯◯ VERY LOW*,†
				3-year survival rate	21	RR 2 (0.15-27.45)	⊕◯◯◯ VERY LOW*,†
‡Sorafenib vs. sorafenib-TACE	Observational study	1	Class 5 (49.4%), 6 (26.9%), and 7 (23.6%)	Overall survival	89	HR 1.17 (0.52-1.80)	⊕◯◯◯ VERY LOW*,†
‡RT vs. sorafenib	Observational study	1	Class A (100%)	1-year survival	56	RR 1.3 (0.67-2.70)	⊕◯◯◯ VERY LOW*,†
‡HAIC vs. sorafenib	Observational study	1	Class A (83.6%) Class B (16.4%)	Mortality	110	RR 0.94 (0.79-1.21)	⊕◯◯◯ VERY LOW*,†

*Serious risk of bias.
†Imprecision.
‡Studies included only PVTT.
Abbreviations: NR, not reported; ES, effect size.

TABLE 6. Summary of Evidence for Outcomes Reported in Studies With Metastatic Disease

Intervention vs. comparison	Design	Studies (n)	Child-Pugh	Outcome	Patients (n)	ES (95% CI)	GRADE
Sorafenib vs. Placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	309	HR 0.84 (0.67-1.1), $I^2 = 0\%$	⊕⊕⊕◯ MODERATE†
Cytotoxic chemotherapy vs. sorafenib	Observational study	1	Class A (76.1%) Class B (23.9%)	Overall Survival	66	HR 0.7 (0.2-1.9)	⊕◯◯◯ VERY LOW*†
Chemoembolization with/ without RT vs. sorafinib	Observational study	1	Class A (64.4%) Class B (35.6%)	Overall Survival	101	HR 0.66 (0.43-1.02)	⊕◯◯◯ VERY LOW*†

*Methodological limitations.
†Imprecision.
Abbreviation: ES, effect size; RCT, randomized control trial.

Discussion

MAIN FINDINGS

In this systemic review evaluating the effectiveness of systemic and locoregional treatments in patients with advanced HCC with macrovascular invasion or metastatic/EHS, we identified 14 studies (three RCTs and 11 observational studies). The current evidence suggests that systemic treatment with sorafenib improves OS when compared to no treatment. The confidence in this statement is supported by two randomized placebo-controlled studies. The use of other treatment modalities, including combinations with sorafenib, TACE, and radioembolization, are not supported with high level of evidence.

STRENGTHS AND LIMITATIONS

The data supporting systemic therapy in advanced HCC comes from large, randomized studies. In addition, numerous prospective phase 3 randomized studies have been completed and are ongoing of new systemic treatments for HCC. The results of these types of studies are required to establish and change standards of care. In practice, the largest limitation has been the lack of evidence of this approach to improve survival in patients with CP B liver disease and advanced HCC. To date, the studies with locoregional therapies have generally not been randomized and are observational. Whereas these studies can generate hypothesis and evidence for clinical decision making, the current studies performed to date have significant bias, limiting broad applicability. Furthermore, since the initial literature search, there have been additional studies evaluating selective internal radiation therapy/Y90. Although most are relatively small, retrospective/case control studies,[24-26] recently the only prospective, randomized study comparing selective internal radiation therapy versus sorafenib (systemic therapy) in patients with advanced liver cancer without EHS that has progressed after TACE did not meet its primary endpoint of improving OS over sorafenib.[27] Also, studies were not excluded based on the appropriateness of the control arms; for example, Yang et al. and Giorgio et al. evaluated cryotherapy and RFA, respectively, in patients with advanced HCC. Together, these data highlight the need for prospective, randomized studies to provide high levels of evidence on how best to integrate new approaches into the management of HCC.[28]

One aspect not captured in this analysis is tolerability and cost. Clearly, any intervention that has improved efficacy must be balanced by the toxicity. The side-effect profile for sorafenib is well established and often is accompanied by dose reductions and delays. The decision to initiate treatment needs to be made after a balanced review of the evidence weighed against the side-effect profile. In addition, the cost of an intervention that is not associated with cure, but a reduction in the risk of death, is often an issue of discussion for patients and the health system.

CLINICAL AND RESEARCH IMPLICATIONS

There is clearly a need for an increased number therapeutic options with higher levels of evidence. Moving forward, there needs to be an emphasis on generating high-quality data not only with systemic therapies, but with locoregional therapies as well. This is feasible and large, randomized, prospective studies have been performed[22] and are ongoing.[23] Though the safety of catheter-based approaches has been established for patients with CP A liver disease, more efficacy data are awaited before these approaches become routine in the

management of advanced HCC. The impact of the degree of liver dysfunction in contributing to outcomes in advanced HCC must always be kept in mind. The safety of sorafenib has been established in patients with CP B liver disease and HCC, but whether it or any intervention can improve the survival of this group of patients is lacking. Ongoing studies need to explore this question for this large group of patients that are often heterogenous in terms of survival. Finally, the clinical complexity of HCC requires a multidisciplinary approach and the recognition that clinical decisions cannot always be made based on available studies, but must be individualized for any given patient taking into account several factors, including the anatomical stage of their disease, liver function, performance status, comorbidities, the treating centers' level of expertise, and patient preferences.

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