OPEN

Hepatic Resection as a Safe and Effective Treatment for Hepatocellular Carcinoma Involving a Single Large Tumor, Multiple Tumors, or Macrovascular Invasion

Jian-Hong Zhong, MD, A. Chapin Rodríguez, PhD, Yang Ke, MD, Yan-Yan Wang, MD, Lin Wang, PhD, and Le-Qun Li, PhD

Abstract: This systematic review examined whether the available evidence justifies using hepatic resection (HR) during later stages of hepatocellular carcinoma (HCC), which contravenes treatment guidelines but is current practice at many medical centers.

Official guidelines and retrospective studies recommend different roles for HR for patients with large/multinodular HCC or with HCC involving macrovascular invasion (MVI).

Several databases were systematically searched for studies examining the safety and efficacy of HR for treating HCC involving a single large tumor (>5 cm) or multiple tumors, or for treating HCC involving MVI.

We identified 50 studies involving 14 808 patients that investigated the use of HR to treat large/multinodular HCC, and 24 studies with 4389 patients that investigated HR to treat HCC with MVI. Median in-hospital mortality for patients with either type of HCC was significantly lower in Asian studies (2.7%) than in non-Asian studies (7.3%, $P < 0.001$). Median overall survival (OS) was significantly higher for all Asian patients with large/multinodular HCC than for all non-Asian patients at both 1 year (81% vs 65%, $P < 0.001$) and 5 years (42% vs 32%, $P < 0.001$). Similar results were obtained for median disease-free survival at 1 year (61% vs 50%, $P < 0.001$) and 5 years (26% vs 24%, $P < 0.001$). However, median OS was similar for Asian and non-Asian patients with HCC involving MVI at 1 year (50% vs 52%, $P = 0.45$) and 5 years (18% vs 14%, $P = 0.94$). There was an upward trend in 5-year OS in patients with either type of HCC.

HR is reasonably safe and effective at treating large/multinodular HCC and HCC with MVI. The available evidence argues for expanding the indications for HR in official treatment guidelines.

(*Medicine* 94(3):e396)

Abbreviations: AASLD = American Association for the Study of Liver Diseases, BCLC = Barcelona Clinic Liver Cancer, DFS = disease-free survival, EASL = European Association for the Study of the Liver, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hepatic resection, MVI = macrovascular invasion, OS = overall survival.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third cause of cancer-related deaths, and its prevalence is expected to increase in coming decades.[1] HCC staging significantly affects treatment decisions and patient prognosis. Of the several staging systems proposed, the Barcelona Clinic Liver Cancer (BCLC) system[2] is the only one recommended by the American Association for the Study of Liver Diseases (AASLD)[3] and the European Association for the Study of the Liver (EASL).[4] Most major HCC staging systems recommend hepatic resection (HR) only for patients with early-stage HCC (BCLC stage A). To be eligible for such treatment, patients usually need to fit the restrictive Milan criteria: HCC involving either a single tumor <5 cm or up to 3 nodules <3 cm, preserved or minimally compromised liver function (Child–Pugh A or B), and no vascular invasion.[3,5] Associations like the AASLD and EASL do not recommend HR for patients in later stages of HCC (BCLC stage B or C), whose disease often involves multiple tumors, macrovascular invasion (MVI), or portal hypertension. Many medical centers also routinely categorize patients with single large tumors (>5 cm) as stage B, although some experts recommend classifying them as stage A.[6,7] HR is contraindicated for stage B and C patients because of the substantial risk that remnant liver function will be insufficient or that the cancer will recur after surgery. Instead, the BCLC system recommends only palliative treatments, in particular transarterial chemoembolization for stage B patients and sorafenib or other drugs for stage C.[3,4]

Despite official recommendations, many clinicians do not restrict HR to early-stage HCC. In fact, studies in various countries have reported it to be an effective treatment option

Editor: Harry Hua-Xiang Xia.
Received: August 28, 2014; revised: November 25, 2014; accepted: November 26, 2014.
From the Department of Hepatobiliary Surgery (J-HZ, ACR, Y-YW, L-QL), Affiliated Tumor Hospital of Guangxi Medical University, Nanning; Department of Research (ACR), Creaducate Enterprises Ltd, Kowloon, Hong Kong; and Department of Hepatobiliary Surgery (YK, LW), The Second Affiliated Hospital of Kunming Medical University, Kunming, PR China.
Correspondence: Le-Qun Li, Hepatobiliary Surgery Department, Affiliated Tumor Hospital of Guangxi Medical University, He Di Rd. #71, Nanning 530021, PR China (e-mail: zhongjianhong66@163.com).
Drs Jian-Hong Zhong and A. Chapin Rodríguez contributed equally to the writing of this article.
J-HZ conceived the study, and J-HZ and ACR designed the search strategy and statistical analysis. J-HZ, YK, LW and Y-YW collected the data, whereas ACR checked the data against the original publications. J-HZ and ACR drafted and revised the manuscript. J-HZ and L-QL are guarantors of the study. All authors had full access to all the data in the study and can take responsibility for data integrity and accuracy of the data analysis. All authors approved the final version of the article.
This study was supported by the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province (nos. Z2012345 and Z2014241) and Youth Science Foundation of Guangxi Medical University (no. GXMUYSF201302) to J-HZ, and National Science and Technology major special project (2012ZX10002010001009) and the National Natural Science Foundation of China (no. 81160262/H1602) to L-QL. The funding sources had no role in the design or conduct of the study; in the collection, analysis or interpretation of the data; or in the preparation, review, or approval of the manuscript.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000396

TABLE 1. Demographics and Clinicopathology of Patients with Hepatocellular Carcinoma Involving Large and/or Multiple Tumors Treated by Hepatic Resection

					Liver Function, n (%)		Comorbidities, n (%)		
Study	**Country**	**Total Patients***	**Single Tumor, n (%)**	**Tumor Size (cm)†**	**Child–Pugh A**	**Cirrhosis**	**HBV**	**HCV**	**Notes**
Abdel-Wahab et al[15]	Egypt	20	–	6.9 ± 1.5	14 (70)	18 (90)	3 (15)	14 (70)	Tumor size 5–10 cm
		18	–	15.2 ± 3.8	13 (72)	15 (83)	3 (17)	13 (72)	Tumor size ≥10 cm
Allemann et al[16]	Switzerland	22	–	13.5 (10–21)	22 (100)	9 (41)	4/9 (45)	2/9 (22)	Tumor size ≥10 cm
Ariizumi et al[17]	Japan	177	63 (36)	13 (10–24)	143 (81)	35 (20)	60 (34)	117 (66)	Tumor size ≥10 cm
Chang et al[18]	Taiwan	318	135 (43)	7.4 (IQR, 5.7–10.4)	311 (98)	97 (31)	201 (64)	57 (19)	BCLC-B
Chen et al[19]	China (central)	525	392 (75)	13.3 ± 2.6	462 (88)	480 (91)	366 (70)	–	Tumor size ≥10 cm
Cheng et al[20]	Taiwan	41	–	8.0 (IQR, 5.5–10.3)	37 (93)	15 (37)	27 (73)	8 (22)	Hemi- or extended hepatectomy
		63	–	6.5 (IQR, 5.5–8.5)	56 (89)	30 (48)	43 (68)	15 (25)	Central hepatectomy
Chirica et al[21]	France	20	3 (15)	6 (2.5–15.0)	20 (100)	12 (60)	6 (30)	6 (30)	Stage IVA (TNM); 7 patients (35%) showed macrovascular invasion
Cho et al[22]	South Korea	61	61 (100)	7.1 ± 1.1	56 (92)	35 (58)	40 (67)	5 (8)	Tumor size >5 cm and <10 cm
Choi et al[23]	South Korea	50	29 (58)	≥10	48 (96)	13 (26)	33 (66)	1 (2)	Tumor size ≥10 cm
Delis et al[24]	Greece	66	51 (77)	8.4 (5.2–11.2)	66 (100)	59 (89)	36 (55)	15 (23)	Tumor size >5 cm
Galun et al[25]	Serbia	32	30 (94)	10.25 (mean)	22 (69)	32 (100)	13 (41)	4 (13)	BCLC-B
Hanazaki et al[26]	Japan	133	104 (78)	8.6 ± 3.8	93 (70)	69 (52)	–	–	Tumor size ≥5 cm
Ho et al[27]	Taiwan	294	0 (0)	5.0 ± 3.5	229/242 (95)	188 (64)	200/281 (71)	82/254 (32)	Tumor number ≥2
Hsu et al[28]	Taiwan	268	160 (60)	≥7: 146‡	248 (93)	–	176 (66)	48 (18)	Beyond Milan criteria; 179 (67%) had macrovascular invasion
Huang et al[29]	Taiwan	139	–	≥10: 104‡	–	80/139 (58)	68/96 (71)	10/96 (11)	Tumor size ≥10 cm, tumor rupture and/or involvement of adjacent organs
Ikai et al[30]	Japan	4972	–	5–10	–	–	–	–	Tumor size 5–10 cm
		2127	0 (0)	>10	–	–	–	–	Tumor size >10 cm
Ishizawa et al[10]	Japan	126	0 (0)	3.5 (1.1–14)	105 (83)	103 (82)	12 (10)	93 (74)	Tumor number ≥2
Lee et al[31]	South Korea	100	80 (80)	13.3 ± 3.0	88 (88)	–	83 (83)	–	Tumor size >10 cm; 22 (22%) had macrovascular invasion
Liau et al[32]	USA	82	71 (87)	14.7 ± 4.1	73/78 (94)	8/80 (10)	–	4 (5)	Tumor size >10 cm
Lin et al[33]	Taiwan	93	49 (53)	8.0 ± 3.3	93 (100)	–	60 (65)	22 (24)	BCLC-B
Liu et al[35]	Hong Kong	54	–	10.3 (5–25)	–	15 (28)	46 (85)	–	Tumor size ≥5 cm; treated using anterior resection approach; 30 (56%) showed ''venous infiltration'' by tumor
		106	–	10.5 (5–18)	–	41 (39)	90 (85)	–	Tumor size ≥5 cm; treated using conventional resection approach; 64 patients (61%) showed ''venous infiltration'' by tumor
Liu et al[34]	Hong Kong	60	41 (68)	10.5 (8–13)	–	19 (32)	55 (92)	2 (3)	Tumor size ≥5 cm; treated by anterior resection approach; 37 patients (62%) showed ''lymphovascular permeation'' by the tumor
		60	41 (68)	10 (7–12.5)	–	19 (32)	51 (85)	1 (2)	Tumor size ≥5 cm; treated by conventional resection approach; 39 patients (65%) showed ''lymphovascular permeation'' by the tumor

Luo et al[36]	China (southern)	85	0 (0)	8.7 ± 3.5	60 (71)	64 (75)	70 (82)	2 (2)	Tumor number ≥2
Mok et al[37]	Taiwan	56	31 (55)	>10	–	28 (50)	43 (77)	16 (29)	Tumor size >10 cm
Nagano et al[38]	Japan	26	15 (58)	>10	22 (85)	5 (19)	14 (54)	3 (12)	Tumor size >10 cm
Ng et al[39]	Hong Kong, USA, France, Japan	380	–	–	361 (95)	101 (27)	281 (74)	20 (5)	Single nodule >5 cm or multiple nodules
Ng et al[40]	Australia	44	23 (52)	12.4 (10–20)	35 (80)	15 (34)	15 (34)	3 (7)	Tumor size ≥10 cm; 13 patients (30%) treated with both resection and ablation
Pandey et al[41]	Singapore	166	95 (57)	13 (10–24)	166 (100)	80 (48)	130 (78)	2 (1)	Tumor size ≥10 cm; 101 patients (61%) treated with both resection and transarterial chemoembolization or ablation
Poon et al[42]	Hong Kong	120	79 (66)	13.8 ± 3.0	–	32 (27)	103 (86)	–	Tumor size >10 cm; 20 patients 17%) had macrovascular invasion
Ramacciato et al[43]	Italy	31	31 (100)	8.2 ± 2.3	16 (52)	25 (81)	7 (23)	9 (29)	Tumor size >5 cm
		20	0 (0)	3.3 ± 1.4	5 (25)	19 (95)	2 (10)	15 (75)	Tumor number ≥3
Ruzzenente et al[44]	Italy	30	0 (0)	–	–	30 (100)	–	–	2–3 nodules
		6	0 (0)	–	–	6 (100)	–	–	≥3 nodules
		46	–	>5	–	46 (100)	–	–	Tumor size >5 cm
Schiffman et al[45]	USA	78	61 (78)	≥5	12 (15)	32 (41)	10 (13)	16 (21)	Tumor size ≥5 cm; 18 patients (23%) had microvascular or macrovascular invasion
Shah et al[46]	Canada	24	–	13.1 ± 2.9	24 (100)	–	9 (38)	1 (4)	Tumor size ≥10 cm; 13 patients (54%) had macrovascular invasion
Shimada et al[47]	Japan	85	37 (44)	12 (10–26)	–	9 (11)	27 (32)	19 (25)	Tumor size ≥10 cm; 31 patients (45%) underwent preoperative transarterial chemoembolization
Shrager et al[48]	USA	130	95 (74)	14.2 ± 3.84	116 (95)	–	56 (43)	23 (18)	Tumor size ≥10 cm; 116 patients (89%) underwent resection; 66 patients (52%) had macrovascular invasion; 23 (18%) were treated with both resection and tumor thrombectomy
Taniai et al[49]	Japan	29	13 (45)	13.5 ± 2.8	23 (79)	12 (41)	6 (21)	17 (59)	Tumor size ≥10 cm; 13 patients (45%) had macrovascular invasion
Torzilli et al[8]	France, Italy, Japan, Argentina, USA	737	–	6 (1–25)	–	360/659 (56)	158/566 (28)	208/566 (37)	BCLC-B
Truant et al[50]	France	52	43 (83)	14 (8–22.9)	–	0 (0)	6 (12)[§]	Tumor size ≥8 cm; 27 patients (52%) had microvascular and/or macrovascular invasion	
Wakabayashi et al[51]	Japan	28	–	6.7 ± 4.1	21 (75)	–	13 (46)	15 (54)	Multiple intrahepatic lesions
Wang et al[52]	Taiwan	112	0 (0)	5–10: 34[‡]					

(continued overleaf)

TABLE 1. (*Continued*)

Study	Country	Total Patients*	Single Tumor, n (%)	Tumor Size (cm)†	Liver Function, n (%)		Comorbidities, n (%)		Notes
					Child–Pugh A	Cirrhosis	HBV	HCV	
>10: 24‡	–	62 (55)	69 (62)	35/99 (35)	Tumor number ≥2; 18 patients (39%) had macrovascular invasion				
Wang et al[54]	Taiwan	243	–	–	–	–	–	–	BCLC-B with multiple or single large (>5 cm) tumors
Wang et al[53]	China (southern)	189	–	5–10: 189‡	–	–	–	–	Tumor size 5–10 cm
		83	–	>10: 83‡	–	–	–	–	Tumor size >10 cm
Yamashita et al[55]	Japan	53	–	13.2 ± 0.4	38 (72)	–	18 (34)	22 (42)	Tumor size ≥10 cm; 24 patients (45%) had macrovascular invasion
Yang et al[56]	China (eastern)	86	–	≥15	–	66 (77)	63 (73)	–	Tumor size ≥15 cm
Yang et al[57]	China (central)	260	260 (100)	9.63 ± 4.07	217 (83)	198 (76)	239 (92)	–	Tumor size >5 cm; 143 patients (55%) had ''vein invasion''
		86	0 (0)	6.98 ± 3.67	60 (70)	71 (83)	80 (93)	–	Tumor number ≥2; 61 patients (71%) had ''vein invasion''
Yin et al[58]	China (eastern)	88	0 (0)	9.5 ± 3.0	87 (99)	69 (78)	81 (92)	3 (3)	Beyond Milan criteria
Young et al[59]	UK	42	24 (57)	14 (10–37)	–	2 (5)	7 (17)§	Tumor size >10 cm; 13 patients (31%) had macrovascular invasion	
Zhong et al[9]	China (southern)‖	660	515 (78)	8.3 (5–20)	660 (100)	514 (78)	614 (93)	13 (2)	BCLC-B
Zhou et al[61]	China (eastern)	621	379 (61)	≥10	–	–	–	–	Tumor size ≥10 cm
Zhou et al[60]	China (northern)	85	85 (100)	>5	80 (94)	65 (76)	68 (80)	6 (7)	Single tumor >5 cm; 6 patients (7%) had macrovascular invasion

BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, HCV = hepatitis C virus, IQR = interquartile range.

* Total number of patients recruited into the study; the total n for clinical assessments (Child–Pugh A, cirrhosis, HBV, HCV), if different, is indicated in the corresponding data fields.

† Reported as mean ± SD, median (range), or median (IQR), unless indicated otherwise.

‡ Number of patients with tumor(s) of the indicated size or size range.

§ HBV or HCV infection.

‖ This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the BCLC-B subgroup were obtained from the authors.

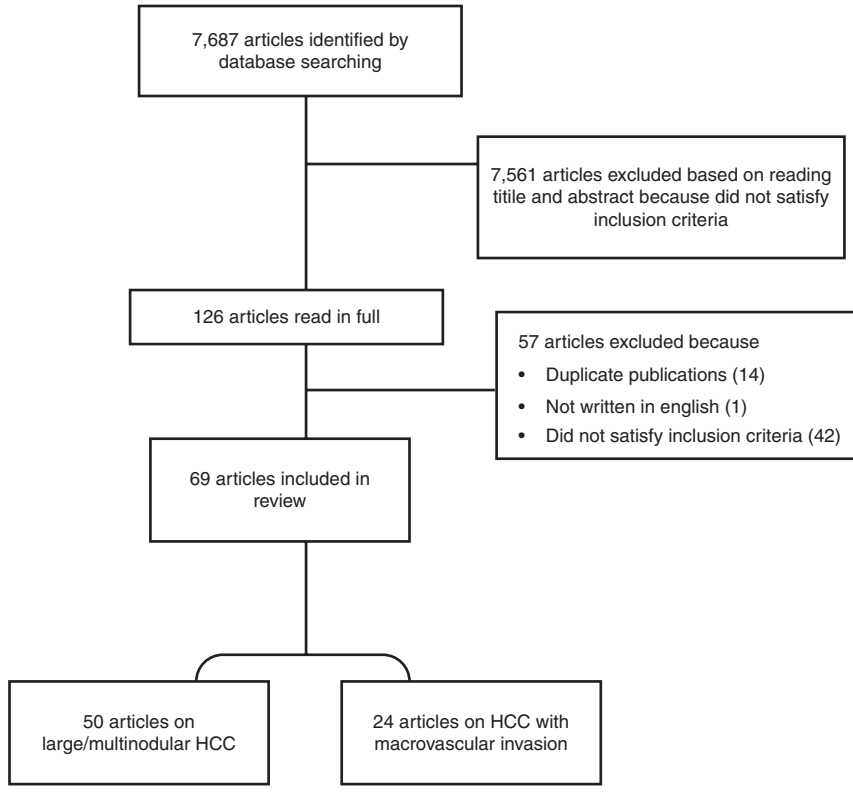

FIGURE 1. Flowchart of study selection. HCC = hepatocellular carcinoma.

for patients in later stages of disease,[8–11] leading to calls to expand the indications for HR.[12] For example, patients with ≥4 nodules in Japan are routinely treated by HR when they show Child–Pugh A or B liver function and no vascular invasion.[13] Consensus-based HCC treatment guidelines of the Japan Society of Hepatology advocate considering HR for a broader range of HCC patients, including those with Child–Pugh B liver function, multiple tumors (regardless of size), or minimal portal invasion.[13]

We are unaware of studies assessing the strength of evidence for or against HR as a treatment for large/multinodular HCC or for HCC with MVI. Here we systematically review the literature on treating such patients with HR, and we find strong evidence that it is a safe and effective therapy for selected patients. Our results suggest that official guidelines should expand the indications for HR to provide more than just palliative options to many currently considered to have unresectable cancer.

METHODS

Database Searching

The following databases were searched for original research articles through the end of March 2014: *PubMed*, the *Cochrane Database of Systematic Reviews*, the *Directory of Open-Acess Journals* (www.doaj.org), and the *Web of Knowledge*. The following search string was used: ''hepatoma'' or ''liver cancer'' or ''liver neoplasm'' or ''liver tumor'' or ''hepatocellular carcinoma'' AND ''resection'' or ''hepatectomy'' or ''surgery'' AND ''intermediate'' or ''advanced'' or ''huge'' or ''large'' or ''multinodular'' or ''vascular invasion''.

Study Inclusion Criteria

Studies were included in our review if they evaluated the efficacy of HR to treat adults with primary HCC involving a single large tumor (>5 cm) or multiple tumors of any size, or to treat adults with HCC involving MVI; reported data on at least one of the outcomes of in-hospital mortality, median survival, overall survival (OS) and disease-free survival (DFS); and were published in English on or after January 1, 2000. In the case of multiple studies based on the same population, we selected the study with the largest number of participants.

Studies were excluded if they evaluated HR specifically as a treatment for recurrent HCC or HCC with microvascular invasion. Although difficult to detect before surgery, microvascular invasion can be diagnosed by postoperative histopathology, but this is not routine clinical practice and so was not performed in many of the studies we found in the literature.

Definitions

HCC in the included studies was diagnosed based on pathology. Large HCC was diagnosed by preoperative imaging and then confirmed histologically as a single tumor >5 cm in diameter with no evidence of additional tumors. MVI was defined as tumor invasion of 1 or more of the following: segmental branches, right/left and main portal vein, hepatic vein, superior mesenteric vein, and inferior vena cava.

OS was measured from when HR was performed until death or the end of follow-up. DFS was measured from when HR was performed until a diagnosis of recurrence. Postoperative complications were those reported to occur within 30 days of surgery.

TABLE 2. Demographics and Clinicopathology of Patients With HCC Involving Macrovascular Invasion Treated by Hepatic Resection

Study	Country	Total Patients *	Single Tumor, n (%)	Tumor † Size, cm	Liver Function, n (%)		Comorbidities, n (%)		Characteristics of Vascular Invasion
					Child–Pugh A	Cirrhosis	HBV	HCV	
Ban et al[62]	Japan	45	–	≥7.0: 24‡	38 (84)	–	19 (42)	15 (33)	Including the main portal vein
Chang et al[18]	Taiwan	160	36 (23)	7.5 (5.0–11.0)	156 (98)	60 (40)	112 (72)	20 (13)	BCLC-C
Chen et al[64]	China (central)	438	362 (83)	7.7 and 8.1§ (2.5–19.2)	–	–	267 (61)	–	PVTT
Chen et al[63]	China (southern)	88	45 (51)	10.1 ± 3.5	74 (84)	73 (83)	79 (90)	3 (3)	PVTT
Fan et al[65]	China (eastern)	84	58 (69)	≥10: 39‡	66 (79)	–	–	–	PVTT; all patients treated with both resection and adjunct chemotherapy
Huang et al[66]	China (western)	116	–	20.7 ± 4.8	116 (100)	41 (35)	90 (78)	2 (2)	Involving the main branches of the PV or HV; 62 patients (53%) treated with both resection and transarterial chemoembolization
Ikai et al[30]	Japan	976	–	–	–	––	–	–	Involving the first-order branches or main trunk of PV
Inoue et al[67]	Japan	49	–	–	42 (86)	–	16 (33)	27 (55)	PVTT
Le Treut et al[68]	France	26	–	9 (3–24)	26 (100)	17 (65)	12 (46)‖	Involving the major PV	
Liang et al[69]	China (southern)	53	33 (62)	≥10: 27‡	37 (70)	41 (77)	49 (92)	–	PVTT
Ohkubo et al[70]	Japan	47	19 (40)	≥10: 15‡	43 (91)	17 (36)	25 (53)	16 (34)	PVTT
Pawlik et al[71]	USA, France, Hong Kong, China, Japan	102	43 (42)	10 (2–22)	92 (90)	–	–	–	Involving the major PV or HV
Peng et al[72]	China (southern)	63	–	9.0 ± 3.0	58 (92)	49 (78)	37 (59)	4 (6)	PVTT
Peng et al[73]	China (southern)	201	95 (47)	>5: 125‡	197 (98)	176 (88)	172 (86)	4 (2)	PVTT
Poon et al[74]	Hong Kong	20	–	8.6 ± 3.6	–	11 (55)	17 (85)	–	Involving the major PV or HV; 2 patients (10%) received postoperative chemotherapy
Roayaie et al[75]	USA	165	–	9.0 ± 5.6	165 (100)	112 (68)	61 (37)	70 (42)	Macrovascular invasion
Ruzzenente et al[44]	Italy	73	–	–	–	73 (100)	–	–	Macrovascular invasion
Shi et al[76]	China (eastern)	406	–	≥5: 376‡	397 (98)	320 (79)	354 (87)	3 (1)	PVTT
Tang et al[77]	China (eastern)	186	101 (54)	9.5 ± 3.4	171 (92)	149 (80)	159 (85)	23 (12)	PVTT; all patients received postoperative transarterial chemoembolization
Torzilli et al, 2013	France, Italy, Japan, Argentina, USA	297	–	6 (1–30)	–	169/265 (64)	70/244 (29)	109/244 (45)	BCLC-C
Wang et al[78]	Taiwan	68	–	–	68 (100)	–	48 (71)	6 (9)	BCLC-C
Wu et al[79]	Taiwan	97	–	8.8 ± 5.1	84 (87)	70 (72)	67 (69)	25 (26)	PVTT
Zhong et al[9]	China¶ (southern)	248	159 (64)	8.7 (1–20)	248 (100)	198 (80)	226 (91)	5 (2)	Macrovascular invasion
Zhou et al[80]	China (eastern)	381	250 (66)	>5: 334‡	–	340 (89)	343 (90)	–	PVTT

BCLC = Barcelona Clinic liver cancer stage, HV = hepatic vein, PV = portal vein, PVTT = portal vein tumor thrombus.
* Total no. of patients recruited into the study; the total n for clinical assessments (Child–Pugh A, cirrhosis, HBV, HCV), if different, is indicated in the corresponding data fields.
† Reported as mean ± SD or as median (minimum to maximum), unless indicated otherwise.
‡ Number of patients with the indicated size or size range.
§ Reported separately for 2 subgroups with PVTT, which were combined for the purposes of our review.
‖ HBV or HCV infection.
¶ This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the BCLC-C subgroup were obtained from the authors.

Data Extraction and Analysis

Four authors (J.-H.Z., Y.K., L.W., Y.Y.W.) extracted data from included studies using a predefined template, and a sixth author (A.C.R.) checked the extracted data against the original articles. Data were extracted on demographic and clinicopathological characteristics of patients, in-hospital mortality, postoperative complications, and both OS and DFS at 1, 3, and 5 years after HR. Survival data were taken directly from tables or the text whenever possible; if such data were presented only in graphs, they were extracted by manual interpolation.

Study-level data were analyzed using simple descriptive statistics (mean, median, range) after aggregating studies based on type of HCC (large/multinodular vs MVI) or patient ethnicity (Asian vs non-Asian). Differences between continuous data were analyzed using the sample size-weighted Mann–Whitney *U* test. Differences between categorical data were analyzed using the chi-squared test. For the included studies, 1-, 3- and 5-year OS and DFS were summarized graphically using bubble plots, in which relative sample size was proportional to bubble size.[14] Changes in 5-year OS over time were analyzed using least-squares weighted regression according to sample

size as implemented in Microsoft Excel 2013 for personal computer.

RESULTS

Our systematic review identified 50 studies[8–10,15–61] involving 14,808 participants investigating the efficacy and/or safety of HR to treat multinodular HCC, defined as involving multiple tumors regardless of size, or to treat large HCC, defined as involving a single tumor >5 cm (Table 1, Figure 1). Whereas most studies of large HCC used the cut-off of 5 cm, some focused specifically on so-called ''huge'' or ''giant'' HCC involving tumors ≥10 cm. Most studies on large/multinodular HCC examined patients who had been treated only with HR, whereas some studies included patients who had been treated with a combination of HR and adjunct therapy. Some of the included studies contained a substantial proportion of patients with MVI, but their outcomes data were usually aggregated with those of patients without such invasion.

We also identified 24 studies[8,9,18,30,44,62–80] with 4389 participants investigating the efficacy and/or safety of HR to treat HCC involving MVI (Table 2). In these studies, all patients had MVI.

Heterogeneity of patient clinicopathology and treatment across the included studies precluded pooling the data and performing meta-analyses. Instead, study-level data were analyzed using simple descriptive statistics after aggregating studies based on type of HCC (large/multinodular vs MVI) or patient ethnicity (Asian vs non-Asian). Three studies were excluded from ethnic subgroup analysis because the cohorts included patients from Asian and non-Asian countries, and data for each ethnic group were not reported separately.[8,39,71]

In both sets of studies for large/multinodular HCC and for HCC with MVI, most patients were from Asia, and the midpoints of the enrollment periods fell between 1990 and 2005 (Tables 3 and 4). Most patients had preserved liver function (Child–Pugh A). The median rate of cirrhosis was 57% (range, 11%–91%) in Asian studies, lower than the 81% (range, 0%–100%) in non-Asian studies ($P = 0.21$). Cirrhosis was significantly more frequent among Asian patients with HCC with MVI (median, 78%; range, 35–89%) than among Asian patients with large/multinodular HCC (median, 50%; range, 11%–91%; $P = 0.025$). Otherwise, we did not observe significant differences in cirrhosis frequency between the 2 ethnic groups or HCC types.

The median rate of hepatitis B virus (HBV) infection was 75% (range, 10%–93%) in Asian patients with either type of HCC, significantly higher than the 32% (range, 10%–55%) in non-Asian patients ($P < 0.001$). Conversely to the trend with HBV infection, the median rate of hepatitis C virus (HCV) infection in Asian patients was 16% (range, 1%–74%), significantly lower than the 25% (range, 4%–75%) in non-Asian patients ($P < 0.001$).

Postoperative Complications

The postoperative complications observed most frequently in our cohorts were bleeding, sepsis, intraabdominal abscess, liver insufficiency, ascites, cardiac and pulmonary complications, and biliary leakage. When patients of Asian and non-Asian ethnicity were aggregated, the complication rate was found to be only slightly higher in those with HCC involving MVI (median, 30.2%; range, 4.0%–42.0%) than in those with large/multinodular HCC (median, 27.0%; range, 1.6%–72%; $P = 0.176$). When patients with either type of HCC were aggregated, the complication rate was significantly lower for Asian patients (median, 26.8%; range, 1.6%–40.3%) than for non-Asian ones (median, 32.3%; range, 21.5%–72.0%; $P < 0.001$).

In-Hospital Mortality

When patients of Asian and non-Asian ethnicity were aggregated, in-hospital mortality was found to be similar for patients with large/multinodular HCC (median, 2.7%; range, 0%–18%) and for those with HCC involving MVI (median, 2.7%; range, 0%–24%; $P = 0.73$). When patients with either type of HCC were aggregated, in-hospital mortality was found to be significantly lower for Asian patients (median, 2.7%; range, 0%–24%) than for non-Asian ones (median, 7.3%; range, 0%–18%; $P < 0.001$). This difference was due almost entirely to the mortality difference between Asian and non-Asian patients with large/multinodular HCC, as only 2 studies of non-Asian HCC patients with MVI were included in our review.

Overall and Disease-Free Survival Across All Studies

Median OS across all studies investigating large/multinodular HCC decreased from approximately 81% at 1 year to 42% at 5 years (Figure 2). Median OS across all studies investigating HCC with MVI decreased from approximately 50% at 1 year to 18% at 5 years.

Median DFS across all studies investigating HCC with large/multinodular HCC fell from 61% at 1 year to 26% at 5 years (Figure 3). The corresponding DFS rates for HCC with MVI were 32% and 18%.

Overall Survival by Patient Ethnicity and Type of HCC

Given the notable differences between Western and Asian attitudes toward using HR for later-stage HCC, we compared survival outcomes separately in Asian and non-Asian cohorts.

OS at 1 year after surgery to treat large/multinodular HCC was significantly higher among Asian patients (median, 81%; range, 41%–94%) than among non-Asian patients (median, 65%; range, 50%–73%; $P < 0.001$). The same trend was observed at 5 years after surgery: OS for Asian patients (median, 42%; range, 17%–66%) was significantly higher than for non-Asian patients (median, 32%; range, 0%–56%; $P < 0.001$).

In contrast, 1-year OS after surgery to treat HCC with MVI was similar for Asian patients (median, 50%; range, 18%–81%) and non-Asian patients (median, 52%; range, 38%–52%; $P = 0.45$). The same trend was observed at 5 years after surgery: OS for Asian patients (median, 18%; range, 2%–40%) was similar to that for non-Asian patients (median, 14%; range, 13%–20%; $P = 0.94$).

Disease-Free Survival by Patient Ethnicity and Type of HCC

Among patients with large/multinodular HCC, median 1-year DFS was 61% (range, 28%–82%) for Asian patients, compared with 50% (range, 32%–62%) for non-Asian patients ($P < 0.001$). The same trend was observed for 5-year DFS, although these rates were substantially lower than at 1 year: median survival was 26% (range, 10%–39%) for Asian patients, compared with 24% (range, 0%–43%) for non-Asian patients ($P < 0.001$).

How median DFS compares between Asian and non-Asian patients with HCC and MVI is unclear, as only 1 non-Asian

TABLE 3. Postoperative Complications, In-Hospital Mortality and Survival of Patients With Hepatocellular Carcinoma Involving Large and/or Multiple Tumors After Hepatic Resection

Study	Enrollment period	Total Patients	Postoperative Complications, %	In-Hospital Mortality, %	Median Survival, mo	OS, %			DFS, %		
						1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Abdel-Wahab et al[15]	1993–1998	20	*ca.* 35.0	5.0	–	70	10	–	–	–	–
		18	*ca.* 72.0	11.1	–	50	0	–	–	–	–
Allemann et al[16]	1997–2009	22	23.0	0*	27	–	–	45	–	–	27
Ariizumi et al[17]	1990–2008	177	–	5.6	–	61	46	42	–	–	29*
Chang et al[18]	1991–2006	318	–	*ca.* 2.7†	–	81	59	47	*ca.* 56	*ca.* 39	29
Chen et al[19]	1972–2000	525	26.8	2.7†	–	*ca.* 70	34	17	–	–	–
Cheng et al[20]	1999–2005	41	14.6	7.3†	–	90	–	66	50	–	39
		63	12.7	7.9†	–	88	–	53	50	–	15
Chirica et al[21]	1998–2004	20	30.0	5.0	32	73	56	45	40	20	17
Cho et al[22]	1998–2001	61	1.6	1.6	–	85	59	53	58	40	32
Choi et al[23]	1996–2006	50	24.0	0	–	70	50	40	49	39	39
Delis et al[24]	2002–2008	66	*ca.* 27.2	0	36	69	37	32	60	33	29
Galun et al[25]	2001–2008	32	62.5	0	26	–	–	–	–	–	–
Hanazaki et al[26]	1983–1997	133	33.8	10.5†	–	–	38	28	–	26	20
Ho et al[27]	1981–2000	294	–	–	38	77	52	37	*ca.* 61	*ca.* 32	*ca.* 25
Hsu et al[28]	2002–2010	268	*ca.* 20.0	2.7‡	–	81	63	43	–	–	–
Huang, et al[29]	2001–2005	139	9.4	*ca.* 4.3	20.4	62	39	29	*ca.* 41	*ca.* 23	*ca.* 19
Ikai et al[30]	1992–2003	4972	–	–	–	81	56	42	–	–	–
		2127	–	–	–	67	43	32	–	–	–
Ishizawa et al[10]	1994–2004	105	15.0	0	–	–	72	58	–	*ca.* 27	*ca.* 25
		21		0	–	–	33	19	–	*ca.* 13	*ca.* 0
Lee et al[31]	1997–2003	100	–	2.0	–	66	44	31	43	26	20
Liau et al[32]	1985–2002	82	50.0	2.4†	32	–	–	33	–	–	24
Lin et al[33]	2001–2007	93	–	5.4	27.6	83	49	–	–	–	–
Liu et al[35]	1989–1997	54	42.6	0	59.7	–	–	–	–	–	–
		106	44.3	13.2	18.6	–	–	–	–	–	–
Liu et al[34]	1999–2004	60	26.7	1.7	>68.1	–	–	–	–	–	–
		60	33.3	10.0	22.6	–	–	–	–	–	–
Luo et al[36]	2004–2006	85	29.4	2.4	22.5	71	35	24	–	–	–
Mok et al[37]	1990–2001	56	*ca.* 7.1	1.8	17	61	25	25	*ca.* 28	*ca.* 20	*ca.* 20
Nagano et al[38]	1985–2001	26	30.8	3.8	10.1	41	29	29	*ca.* 65	*ca.* 49	–
Ng et al[39]	1982–2001	380	27.0	2.4	36.9	74	50	39	54	38	26
Ng et al[40]	1990–2008	44	–	18.2	21.5	66	38	28	50	24	19
Pandey et al[41]	1995–2006	166	–	3.0†	20	*ca.* 68	*ca.* 35	29	–	–	–
Poon et al[42]	1991–2000	120	35.0	5.0†	18.8	61	38	28	32	14	10
Ramacciato et al[43]	2000–2006	31	32.3	16.1†	68	–	–	56	–	–	41
		20	25.0	15.0†	23	–	–	34	–	–	0
Ruzzenente et al[44]	1991–2007	30	–	–	58	–	–	46	–	–	–
		6	–	–	10	–	–	0	–	–	–
		46	–	–	32	–	–	29	–	–	–
Schiffman et al[45]	1999–2005	78	41.0	24.4‡	20	*ca.* 65	*ca.* 33	*ca.* 16	*ca.* 52	*ca.* 26	*ca.* 13
Shah et al[46]	1993–2004	24	50.0	8.3‡	–	*ca.* 69	*ca.* 62	54	*ca.* 37	*ca.* 21	–
Shimada et al[47]	1988–2004	86	–	1.2	27.6	–	–	32	–	–	–
Shrager et al[48]	1992–2010	130	21.5	6.9†	17.0	57	30	19	*ca.* 32	*ca.* 13	*ca.* 12
Taniai et al[49]	1987–2006	29	27.6	6.9†	–	52	34	34	48	22	22
Torzilli et al[8]	1990–2009	737	*ca.* 42.0	3.1†	–	88	71	57	63	38	27
Truant et al[50]	2000–2010	52	26.9	9.6‡	–	–	–	43	–	–	39
Wakabayashi et al[51]	1990–2001	28	–	–	19	58	27	22	–	–	–
Wang et al[52]	1990–2006	112	–	*ca.* 2.7	47	86	56	30	46	29	18
Wang et al[54]	1986–2002	243	–	–	60.4	82	64	51	–	–	–
Wang et al[53]	1991–2004	189	–	–	–	70	51	37	–	–	–
		83	–	–	–	47	25	20	–	–	–
Yamashita et al[55]	1995–2007	53	24.5	3.8	–	74	43	35	–	–	*ca.* 24
Yang et al[56]	1985–1996	86	31.4	3.5†	–	58	36	18	–	–	–
Yang et al[57]	1992–2002	260	18.5	2.3†	45.5	87	56	38	82	51	35
		86	17.4	2.3†	14.9	78	29	20	63	32	18
Yin et al[58]	2008–2010	88	10.2	*ca.* 1.1	41	76	52	–	–	–	–
Young et al[59]	1994–2006	42	–	–	–	70	45	45	62	49	43
Zhong et al[9]	2000–2007§	660	27.0	2.6	54	91	67	44	–	–	–
Zhou et al[61]	1964–1999	621	–	4.5†	–	68	37	26	–	–	–
Zhou et al[60]	1995–2002	85	–	–	56	94	56	47	74	34	15

ca. = approximately (for data estimated from published graphs or incomplete descriptions in the text) , DFS = disease-free survival, OS = overall survival.

* For 119 patients who underwent curative hepatic resection

† At 1 month

‡ At 3 months

§ This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the subgroup of patients with BCLC-B HCC were obtained from the authors.

TABLE 4. Postoperative Complications, In-Hospital Mortality and Survival of Patients With Hepatocellular Carcinoma Involving Macrovascular Invasion Treated by Hepatic Resection

Study	Enrollment period	Total Patients	Postoperative Complications, %	In-hospital Mortality, %	Median Survival, mo	OS, %			DFS, %		
						1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Ban et al[62]	1992–2008	45	22.2	0	20	70	37	22	30	21	0
Chang et al[18]	1991–2006	160	–	2.7*	*ca.* 22	58	34	29	*ca.* 32	*ca.* 24	22
Chen et al[64]	1990–2003	438	17.4	0/2.6†	19/10*	52	16	12	–	–	–
Chen et al[63]	2006–2008	88	19.3	4.5	9	31	15	–	–	–	–
Fan et al[65]	1997–2002	84	–	–	15	39	16	–	–	–	–
Huang et al[66]	1998–2008	116	30.2	3.4	*ca.* 21	71	23	11	48	16	4
Ikai et al[30]	1992–2003	976	–	–	*ca.* 12	50	26	18	–	–	–
Inoue et al[67]	1995–2006	49	–	0	*ca.* 34	60	45	40	35	30	20
Le Treut et al[68]	1998–2004	26	38.5	11.5	9	38	20	13	–	–	–
Liang et al[69]	2001–2005	53	–	1.9	6	23	6	–	8	4	–
Ohkubo et al[70]	1985–1997	47	–	2.1	–	54	33	24	31	18	–
Pawlik et al[71]	1984–1999	102	–	5.9	11	45	17	10	–	–	–
Peng et al[72]	1997–2001	63	–	1.9	7.8	18	15	2	–	–	–
Peng et al[73]	2002–2007	201	4.0	0.5	20	42	14	11	23	9	3
Poon et al[74]	1989–2000	20	–	5.0	6	30	13	13	15	5	5
Roayaie et al[75]	1992–2010	165	–	7.3	13	*ca.* 52	*ca.* 22	14	*ca.* 40	*ca.* 20	18
Ruzzenente et al[44]	1991–2007	17	–	–	10	–	–	20	–	–	–
Shi et al[76]	2001–2003	406	32.8	0.2	–	34	13	–	13	5	–
Tang et al[77]	2006–2008	186	36.0	23.7	10	40	14	–	32	6	–
Torzilli et al[8]	1990–2009	297	*ca.* 42.0	3	*ca.* 36	76	49	38	46	28	18
Wang et al[78]	2003–2008	68	–	0	33	55	–	–	–	–	–
Wu et al[79]	1990–1998	15	40.0	0	*ca.* 24	*ca.* 81	*ca.* 45	26	*ca.* 54	*ca.* 32	21
Zhong et al[9]	2000–2007‡	248	*ca.*27.0	4.4	–	81	46	20	55	29	20
Zhou et al[61]	1980–2002	381	–	–	*ca.* 9	47	16	12	–	–	–

ca. = approximately (for data estimated from published graphs), DFS = disease-free survival, OS = overall survival.

* Including intermediate and advanced stage hepatocellular carcinoma (BCLC stages not reported)

† The first value refers to 286 patients in whom portal vein tumor thrombosis occurred within the resected area or within 1 cm from the resection edge and extended into the first branch of the main portal vein. The second value refers to 152 patients in whom portal vein tumor thrombus extended into the main portal vein.

‡ This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the subgroup of patients with BCLC-C HCC were obtained from the authors.

study on this type of HCC was included in the subgroup analysis.[75] Among Asian patients, 1-year median DFS was 32% (range, 8%–55%), whereas 5-year median DFS was 18% (range, 0–22%).

Survival Over Time

Given striking advances in HCC diagnosis, treatment and management in recent decades, we wanted to know whether the efficacy of HR in our cohorts has changed over the 4 decades spanned by the included studies. OS at 5 years showed an upward trend for patients with either type of HCC (Figure 4). A similar upward trend was observed in DFS at 5 years for patients with large/multinodular HCC, whereas DFS did not change appreciably for patients with MVI (data not shown).

DISCUSSION

Official HCC staging systems and clinical practice guidelines, such as those adopted by the AASLD and EASL, recommend HR only for early-stage HCC, even though medical centers around the world also use the procedure to treat patients

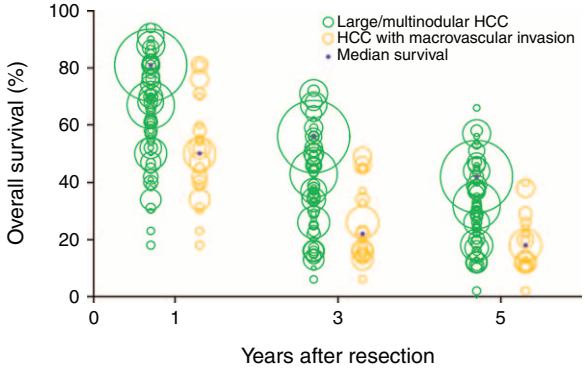

FIGURE 2. Overall survival of patients with large/multinodular HCC or HCC with macrovascular invasion at 1, 3, and 5 years after surgery. HCC = hepatocellular carcinoma.

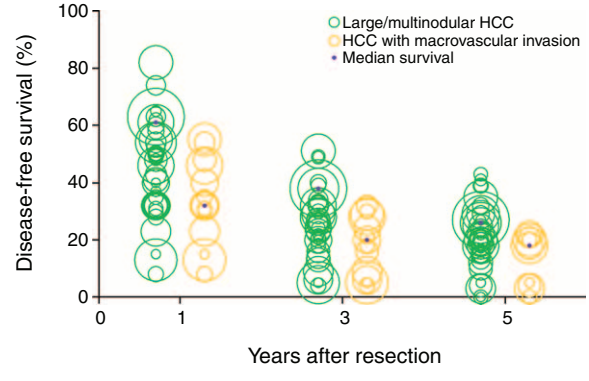

FIGURE 3. Disease-free survival of patients with large/multinodular HCC or HCC with macrovascular invasion at 1, 3, and 5 years after surgery. HCC = hepatocellular carcinoma.

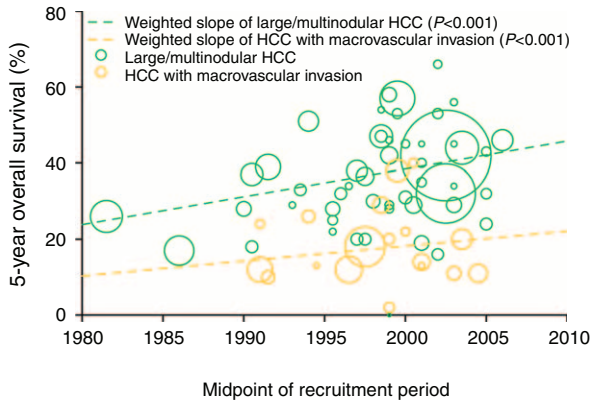

FIGURE 4. Trend in 5-year overall survival of patients with large/multinodular HCC or HCC with macrovascular invasion. HCC = hepatocellular carcinoma.

with later stages of disease. Here we systematically examine the evidence for using HR to treat some types of classically ''unresectable'' HCC, and we find that the procedure can be safe and effective. These results argue for expanding the indications for HR.

Most treatment guidelines do not recommend HR for HCC involving multiple tumors because such patients are considered to be at high risk of intrahepatic and extrahepatic spread. Our results show that HR can be safe and effective in such patients. We also found HR to be safe and effective for patients with a single large tumor (>5 cm). AASLD and EASL guidelines neither unambiguously exclude nor recommend HR for patients with a single large tumor, and surgeons around the world routinely classify them as BCLC stage B and, therefore, unresectable.[6,7] Regardless of whether these patients should be categorized as stage A or B, our findings suggest that they can be treated effectively with HR. Our results are consistent with those of a systematic review[81] examining the prognosis of patients with single or multinodular large HCC; in that study, large HCC was defined more restrictively as at least 1 tumor >10 cm, rather than >5 cm in our review, and those authors considered studies published since 1992, whereas we excluded anything published before 2000.

Thus, our findings are consistent with the suggestion that HR can be effective independently of tumor size, number, and MVI.[82] In fact, the median in-hospital mortality in our studies, which ranged from 2.7% to 7.3% depending on the ethnicity or type of HCC, is comparable to the 4.0% reported in a meta-analysis of 69 studies in which Asian and non-Asian patients with HCC in various stages were treated using resection.[83] The median rate of postoperative complications in our study, which ranged from 26.8% to 32.3% depending on the ethnicity or type of HCC, is also comparable to the 28.1% reported in that study.[83] Among all patients with large/multinodular HCC in our review, 5-year OS was 42% and 5-year DFS was 26%. These figures are certainly lower than the corresponding 5-year OS of 67% and DFS of 37% for patients with early-stage HCC,[14] but they are not even 2-fold lower, suggesting that HR can be considered not only a reasonable but also an effective approach in carefully selected patients with advanced HCC.

HCC spreads primarily by invading the portal vein, resulting initially in intrahepatic metastases and later in extrahepatic ones.[84] Vascular invasion, whether macro or micro, predicts HCC recurrence.[4] We found that HR can be safe and effective for patients with MVI, in contrast to the officially recommended alternatives, such as ablative therapies, transplantation, and systemic chemotherapy, which show no survival benefit in many patients.[82] Thus, HR may be the most promising option for patients with vascular invasion.

This systematic review provides the most updated and comprehensive examination of the use of HR to treat large/multinodular HCC and HCC involving MVI. Its strength lies in the large numbers and ethnic diversity of patients involved, but its weakness lies in the diversity of disease profiles and treatment approaches, which prevented us from pooling and meta-analyzing the data. Therefore, we limited our analysis to simple descriptive statistics to compare subgroups of Asian and non-Asian patients and subgroups of patients with either type of HCC. In addition, we focused only on overall outcomes of in-hospital mortality, postoperative complications, OS, and DFS. Although this approach limits the clinical detail of our review, it still provides a valuable overview of research findings that can inform clinical practice.

The preponderance of Asian cohorts in our included studies likely reflects the fact that HCC is more prevalent in Asian countries and so presents a greater health burden. The Asian cohorts in our review showed higher rates of HBV infection than the non-Asian cohorts, but lower rates of HCV infection. The higher rate of HBV infection is consistent with the fact that the vast majority of Chinese patients with HCC are HBV positive, and Chinese from the mainland, Hong Kong, and Taiwan accounted for more than 60% of all patients in our cohorts. The lower rate of HCV infection contrasts with the high proportion of HCC patients in Japan who are HCV positive[85] and probably reflects the fact that less than one-third of the patients in our cohorts were from that country.

Non-Asian patients in our included studies showed not only a higher rate of HCV infection than Asian patients but also a higher rate of cirrhosis. This is consistent with previous studies showing that most patients (Asian or non-Asian) with both HCV infection and HCC also have advanced fibrosis or cirrhosis.[86,87] These comorbidities may help explain why in-hospital mortality was significantly higher for non-Asian patients than for Asian ones in our review. Consistent with this idea, median OS and DFS were significantly lower for non-Asian patients with large/multinodular HCC than for Asian patients. That liver comorbidities can significantly determine outcomes after HR is supported by a meta-analysis of more than 35,000 resections.[83] This substantial difference in clinical profile between Asian and non-Asian HCC patients in our review may help explain why guidelines from liver associations in the United States and Europe do not recommend HR to treat later stages of HCC, whereas Asian liver centers are less restrictive about using HR.[88–91]At the same time, the difference in prognoses for Asian and non-Asian patients may also reflect differences in numerous other risk factors, including level of α-fetoprotein, stage of tumor differentiation, surgical method, and need for blood transfusion.[41,81]

Portal hypertension is a contraindication for HR according to most treatment guidelines,[3] because it significantly affects prognosis of HCC patients after resection.[92,93] Nevertheless, several studies in our systematic review included substantial proportions of HCC patients with portal hypertension. Our findings suggest that even such patients can be treated safely and effectively by resection. In fact, data from 2 medical centers suggest that it can be a good therapeutic option, giving 5-year OS of 41%[94] and 56%,[10] which compare well with the

corresponding rates of 42% for patients in our cohort with large/multinodular HCC and 18% for patients with MVI.

Analysis of 5-year OS as a function of enrollment period showed a slight upward trend for patients with both types of HCC. These slight increases reflect the stunning drop in perioperative and postoperative mortality associated with HR over the last 20 years.[3,4] This drop is probably due to improved surgical techniques, more sensitive diagnosis of HCC during the asymptomatic phases, and more accurate liver function assessment, allowing physicians to exclude patients at high risk of liver decompensation or death following HR.[95] An increase in OS over time was also reported in a systematic review examining HR to treat early-stage HCC,[14] in a study comparing patients with single or multinodular large HCC treated by HR before or after December 1996,[96] and in a study of patients treated between 1981 and 2008 by hepatectomy of $\geq$4 lobes.[97] Contrary to this trend, we did not observe any clear change in 5-year DFS in our cohort of patients with MVI. This is consistent with the notion that such HCC is a terminal condition with extremely poor prognosis, which is unlikely to change despite improvements in surgical technique or perioperative care.

Recurrence is a major challenge to treat patients with HCC; it occurs in approximately 70% of patients by 5 years after HR,[3,4] and it is the most frequent cause of death among HCC patients after HR. Recurrence can be indirectly assessed by comparing OS and DFS. In our cohorts, median OS at 1 year was 16 to 23 percentage points higher than the corresponding median DFS, depending on whether we compared Asians with non-Asians, or one type of HCC against the other. The corresponding difference between median OS and DFS at 1 year in a systematic review of HR to treat patients with early-stage HCC was on the low end of this range (14 percentage points).[14] By 5 years, the difference between median OS and DFS in our cohorts had fallen to 9 to 12 percentage points, whereas the corresponding difference among patients with early-stage HCC had increased to 30 percentage points.[14] This comparative analysis suggests that using HR in patients with large/multinodular HCC or with HCC involving MVI is not associated with a significant increase in recurrence.

Future studies will need to address a question that our review could not: how much does recurrence contribute to the mortality of patients like ours who show higher prevalence of comorbidities and mortality risk factors than those with early-stage HCC? The generally poorer prognosis for our patients helps explain why median 5-year OS in our cohort, which ranged from 14% to 42% depending on HCC type and patient ethnicity, was lower than the median of 67% (range, 27%–81%) in a systematic review of early-stage HCC treated by HR.[14]

Future research should also focus on refining HR to improve outcomes, reduce recurrence, and increase the range of patients to which it can be applied. These refinements may include 2-stage HR,[98] surgical techniques to prevent large tumor rupture during excision[99] and the combination of HR with percutaneous isolated hepatic perfusion[82,100] or transarterial embolization.[101] The greatest priority may well be reducing the unacceptably high recurrence rate after HR. Although transplantation is usually considered the most effective option for dealing with postresection recurrence,[102] donors are often scarce and as many as 20% of HCC patients on transplant waiting lists must drop out because their cancer progresses beyond transplantation criteria.[103]

While our results indicate that HR can be safe and effective in patients in later stages of HCC, we still recommend that the therapy be considered for each patient on a case-by-case basis. A key parameter to take into account is preoperative liver function: most patients in our cohort had Child–Pugh A function, leaving open the question of whether HR is appropriate for patients with Child–Pugh B or C function. Another consideration is the skill and experience of the surgeon, which can significantly affect the success of HR in complicated HCC.[82,104] We note that Zhang et al[98] and Torzilli et al[105] have developed and validated detailed criteria for deciding whether HR is appropriate for patients in later stages of HCC.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet.* 2003;362:1907–1917.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53:1020–1022.
4. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2012;56:908–943.
5. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334:693–699.
6. Torzilli G, Belghiti J, Kokudo N, et al. Reply to the letter to the editor entitled ''a snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations? an observational study of the HCC East-West Study Group'': when the study setting ''ignores'' the patients. *Ann Surg.* 2013[Epub ahead of print].
7. Torzilli G, Belghiti J, Kokudo N, et al. Reply to the letter to the editor titled ''dissecting EASL/AASLD recommendations with a more careful knife: a comment on 'surgical misinterpretation' of the BCLC staging system'': real misinterpretation or lack of clarity within the BCLC? *Ann Surg.* 2013[Epub ahead of print].
8. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg.* 2013;257:929–937.
9. Zhong JH, Ke Y, Gong WF, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg.* 2014;260:329–340.
10. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology.* 2008;134:1908–1916.
11. Zhong JH, Xiang BD, Gong WF, et al. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS One.* 2013;8:e68193.
12. Livraghi T, Brambilla G, Carnaghi C, et al. Is it time to reconsider the BCLC/AASLD therapeutic flow-chart? *J Surg Oncol.* 2010;102:868–876.
13. Arii S, Sata M, Sakamoto M, et al. Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009). *Hepatol Res.* 2010;40:667–685.
14. Lim KC, Chow PK, Allen JC, et al. Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria. *Br J Surg.* 2012;99:1622–1629.

15. Abdel-Wahab M, Sultan A, el-Ghawalby A, et al. Is resection for large hepatocellular carcinoma in cirrhotic patients beneficial? Study of 38 cases. *Hepatogastroenterology.* 2001;48:757–761.

16. Allemann P, Demartines N, Bouzourene H, et al. Long-term outcome after liver resection for hepatocellular carcinoma larger than 10 cm. *World J Surg.* 2013;37:452–458.

17. Ariizumi S, Kotera Y, Takahashi Y, et al. Impact of hepatectomy for huge solitary hepatocellular carcinoma. *J Surg Oncol.* 2013;107:408–413.

18. Chang WT, Kao WY, Chau GY, et al. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? *Surgery.* 2012;152:809–820.

19. Chen XP, Qiu FZ, Wu ZD, et al. Chinese experience with hepatectomy for huge hepatocellular carcinoma. *Br J Surg.* 2004;91:322–326.

20. Cheng CH, Yu MC, Wu TH, et al. Surgical resection of centrally located large hepatocellular carcinoma. *Chang Gung Med J.* 2012;35:178–191.

21. Chirica M, Scatton O, Massault PP, et al. Treatment of stage IVA hepatocellular carcinoma: should we reappraise the role of surgery? *Arch Surg.* 2008;143:538–543discussion 43.

22. Cho YB, Lee KU, Lee HW, et al. Outcomes of hepatic resection for a single large hepatocellular carcinoma. *World J Surg.* 2007;31:795–801.

23. Choi GH, Han DH, Kim DH, et al. Outcome after curative resection for a huge (>or = 10 cm) hepatocellular carcinoma and prognostic significance of gross tumor classification. *Am J Surg.* 2009;198:693–701.

24. Delis SG, Bakoyiannis A, Tassopoulos N, et al. Hepatic resection for hepatocellular carcinoma exceeding Milan criteria. *Surg Oncol.* 2010;19:200–207.

25. Galun DA, Bulajic P, Zuvela M, et al. Is there any benefit from expanding the criteria for the resection of hepatocellular carcinoma in cirrhotic liver? Experience from a developing country. *World J Surg.* 2012;36:1657–1665.

26. Hanazaki K, Kajikawa S, Shimozawa N, et al. Hepatic resection for large hepatocellular carcinoma. *Am J Surg.* 2001;181:347–353.

27. Ho MC, Huang GT, Tsang YM, et al. Liver resection improves the survival of patients with multiple hepatocellular carcinomas. *Ann Surg Oncol.* 2009;16:848–855.

28. Hsu CY, Hsia CY, Huang YH, et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the Milan criteria: a propensity score analysis. *Ann Surg Oncol.* 2012;19:842–849.

29. Huang JF, Wu SM, Wu TH, et al. Liver resection for complicated hepatocellular carcinoma: challenges but opportunity for long-term survivals. *J Surg Oncol.* 2012;106:959–965.

30. Ikai I, Arii S, Okazaki M, et al. Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. *Hepatol Res.* 2007;37:676–691.

31. Lee SG, Hwang S, Jung JP, et al. Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions. *Br J Surg.* 2007;94:320–326.

32. Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (>10 cm) hepatocellular carcinoma. *Cancer.* 2005;104:1948–1955.

33. Lin CT, Hsu KF, Chen TW, et al. Comparing hepatic resection and transarterial chemoembolization for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma: change for treatment of choice? *World J Surg.* 2010;34:2155–2161.

34. Liu CL, Fan ST, Cheung ST, et al. Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: a prospective randomized controlled study. *Ann Surg.* 2006;244:194–203.

35. Liu CL, Fan ST, Lo CM, et al. Anterior approach for major right hepatic resection for large hepatocellular carcinoma. *Ann Surg.* 2000;232:25–31.

36. Luo J, Peng ZW, Guo RP, et al. Hepatic resection versus transarterial lipiodol chemoembolization as the initial treatment for large, multiple, and resectable hepatocellular carcinomas: a prospective nonrandomized analysis. *Radiology.* 2011;259:286–295.

37. Mok KT, Wang BW, Lo GH, et al. Multimodality management of hepatocellular carcinoma larger than 10 cm. *J Am Coll Surg.* 2003;197:730–738.

38. Nagano Y, Tanaka K, Togo S, et al. Efficacy of hepatic resection for hepatocellular carcinomas larger than 10 cm. *World J Surg.* 2005;29:66–71.

39. Ng KK, Vauthey JN, Pawlik TM, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol.* 2005;12:364–373.

40. Ng KM, Yan TD, Black D, et al. Prognostic determinants for survival after resection/ablation of a large hepatocellular carcinoma. *HPB (Oxford).* 2009;11:311–320.

41. Pandey D, Lee KH, Wai CT, et al. Long term outcome and prognostic factors for large hepatocellular carcinoma (10 cm or more) after surgical resection. *Ann Surg Oncol.* 2007;14:2817–2823.

42. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg.* 2002;194:592–602.

43. Ramacciato G, Mercantini P, Petrucciani N, et al. Does surgical resection have a role in the treatment of large or multinodular hepatocellular carcinoma? *Am Surg.* 2010;76:1189–1197.

44. Ruzzenente A, Capra F, Pachera S, et al. Is liver resection justified in advanced hepatocellular carcinoma? Results of an observational study in 464 patients. *J Gastrointest Surg.* 2009;13:1313–1320.

45. Schiffman SC, Woodall CE, Kooby DA, et al. Factors associated with recurrence and survival following hepatectomy for large hepatocellular carcinoma: a multicenter analysis. *J Surg Oncol.* 2010;101:105–110.

46. Shah SA, Wei AC, Cleary SP, et al. Prognosis and results after resection of very large (>or = 10 cm) hepatocellular carcinoma. *J Gastrointest Surg.* 2007;11:589–595.

47. Shimada K, Sakamoto Y, Esaki M, et al. Role of a hepatectomy for the treatment of large hepatocellular carcinomas measuring 10 cm or larger in diameter. *Langenbecks Arch Surg.* 2008;393:521–526.

48. Shrager B, Jibara GA, Tabrizian P, et al. Resection of large hepatocellular carcinoma (>/ = 10 cm): a unique western perspective. *J Surg Oncol.* 2013;107:111–117.

49. Taniai N, Yoshida H, Tajiri T. Adaptation of hepatectomy for huge hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg.* 2008;15:410–416.

50. Truant S, Boleslawski E, Duhamel A, et al. Tumor size of hepatocellular carcinoma in noncirrhotic liver: a controversial predictive factor for outcome after resection. *Eur J Surg Oncol.* 2012;38:1189–1196.

51. Wakabayashi H, Ushiyama T, Ishimura K, et al. Significance of reduction surgery in multidisciplinary treatment of advanced hepatocellular carcinoma with multiple intrahepatic lesions. *J Surg Oncol.* 2003;82:98–103.

52. Wang BW, Mok KT, Liu SI, et al. Is hepatectomy beneficial in the treatment of multinodular hepatocellular carcinoma? *J Formos Med Assoc.* 2008;107:616–626.
53. Wang J, Xu LB, Liu C, et al. Prognostic factors and outcome of 438 Chinese patients with hepatocellular carcinoma underwent partial hepatectomy in a single center. *World J Surg.* 2010;34:2434–2441.
54. Wang JH, Changchien CS, Hu TH, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma: Survival analysis of 3892 patients. *Eur J Cancer.* 2008;44:1000–1006.
55. Yamashita Y, Taketomi A, Shirabe K, et al. Outcomes of hepatic resection for huge hepatocellular carcinoma (>/= 10 cm in diameter). *J Surg Oncol.* 2011;104:292–298.
56. Yang JM, Kan T, Chen H, et al. Hepatectomy in the treatment of very big primary liver cancer: report of 86 cases. *Hepatobiliary Pancreat Dis Int.* 2002;1:42–45.
57. Yang LY, Fang F, Ou DP, et al. Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. *Ann Surg.* 2009;249:118–123.
58. Yin L, Li H, Li AJ, et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: A RCT. *J Hepatol.* 2014;61:82–88.
59. Young AL, Malik HZ, Abu-Hilal M, et al. Large hepatocellular carcinoma: time to stop preoperative biopsy. *J Am Coll Surg.* 2007;205:453–462.
60. Zhou L, Rui JA, Wang SB, et al. Prognostic factors of solitary large hepatocellular carcinoma: the importance of differentiation grade. *Eur J Surg Oncol.* 2011;37:521–525.
61. Zhou XD, Tang ZY, Ma ZC, et al. Surgery for large primary liver cancer more than 10 cm in diameter. *J Cancer Res Clin Oncol.* 2003;129:543–548.
62. Ban D, Shimada K, Yamamoto Y, et al. Efficacy of a hepatectomy and a tumor thrombectomy for hepatocellular carcinoma with tumor thrombus extending to the main portal vein. *J Gastrointest Surg.* 2009;13:1921–1928.
63. Chen JS, Wang Q, Chen XL, et al. Clinicopathologic characteristics and surgical outcomes of hepatocellular carcinoma with portal vein tumor thrombosis. *J Surg Res.* 2012;175:243–250.
64. Chen XP, Qiu FZ, Wu ZD, et al. Effects of location and extension of portal vein tumor thrombus on long-term outcomes of surgical treatment for hepatocellular carcinoma. *Ann Surg Oncol.* 2006;13:940–946.
65. Fan J, Zhou J, Wu ZQ, et al. Efficacy of different treatment strategies for hepatocellular carcinoma with portal vein tumor thrombosis. *World J Gastroenterol.* 2005;11:1215–1219.
66. Huang J, Hernandez-Alejandro R, Croome KP, et al. Hepatic resection for huge (>15 cm) multinodular HCC with macrovascular invasion. *J Surg Res.* 2012;178:743–750.
67. Inoue Y, Hasegawa K, Ishizawa T, et al. Is there any difference in survival according to the portal tumor thrombectomy method in patients with hepatocellular carcinoma? *Surgery.* 2009;145:9–19.
68. Le Treut YP, Hardwigsen J, Ananian P, et al. Resection of hepatocellular carcinoma with tumor thrombus in the major vasculature. A European case-control series. *J Gastrointest Surg.* 2006;10:855–862.
69. Liang LJ, Hu WJ, Yin XY, et al. Adjuvant intraportal venous chemotherapy for patients with hepatocellular carcinoma and portal vein tumor thrombi following hepatectomy plus portal thrombectomy. *World J Surg.* 2008;32:627–631.
70. Ohkubo T, Yamamoto J, Sugawara Y, et al. Surgical results for hepatocellular carcinoma with macroscopic portal vein tumor thrombosis. *J Am Coll Surg.* 2000;191:657–660.
71. Pawlik TM, Poon RT, Abdalla EK, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. *Surgery.* 2005;137:403–410.
72. Peng B, Liang L, He Q, et al. Surgical treatment for hepatocellular carcinoma with portal vein tumor thrombus. *Hepatogastroenterology.* 2006;53:415–419.
73. Peng ZW, Guo RP, Zhang YJ, et al. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Cancer.* 2012;118:4725–4736.
74. Poon RT, Fan ST, Ng IO, et al. Prognosis after hepatic resection for stage IVA hepatocellular carcinoma: a need for reclassification. *Ann Surg.* 2003;237:376–383.
75. Roayaie S, Jibara G, Taouli B, et al. Resection of hepatocellular carcinoma with macroscopic vascular invasion. *Ann Surg Oncol.* 2013;20:3754–3760.
76. Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Ann Surg Oncol.* 2010;17:2073–2080.
77. Tang QH, Li AJ, Yang GM, et al. Surgical resection versus conformal radiotherapy combined with TACE for resectable hepatocellular carcinoma with portal vein tumor thrombus: a comparative study. *World J Surg.* 2013;37:1362–1370.
78. Wang JH, Kuo YH, Wang CC, et al. Surgical resection improves the survival of selected hepatocellular carcinoma patients in Barcelona clinic liver cancer stage C. *Dig Liver Dis.* 2013;45:510–515.
79. Wu CC, Hsieh SR, Chen JT, et al. An appraisal of liver and portal vein resection for hepatocellular carcinoma with tumor thrombi extending to portal bifurcation. *Arch Surg.* 2000;135:1273–1279.
80. Zhou J, Tang ZY, Wu ZQ, et al. Factors influencing survival in hepatocellular carcinoma patients with macroscopic portal vein tumor thrombosis after surgery, with special reference to time dependency: a single-center experience of 381 cases. *Hepatogastroenterology.* 2006;53:275–280.
81. Tsoulfas G, Mekras A, Agorastou P, et al. Surgical treatment for large hepatocellular carcinoma: does size matter? *ANZ J Surg.* 2012;82:510–517.
82. Truty MJ, Vauthey JN. Surgical resection of high-risk hepatocellular carcinoma: patient selection, preoperative considerations, and operative technique. *Ann Surg Oncol.* 2010;17:1219–1225.
83. Ramacciato G, D'Angelo F, Baldini R, et al. Hepatocellular carcinomas and primary liver tumors as predictive factors for postoperative mortality after liver resection: a meta-analysis of more than 35,000 hepatic resections. *Am Surg.* 2012;78:456–467.
84. Yanaga K. Current status of hepatic resection for hepatocellular carcinoma. *J Gastroenterol.* 2004;39:919–926.
85. Ohishi W, Fujiwara S, Cologne JB, et al. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. *Cancer Epidemiol Biomarkers Prev.* 2008;17:846–854.
86. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology.* 2003;37:429–442.
87. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology.* 2009;136:138–148.

88. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int.* 2010;4:439–474.

89. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis.* 2011;29:339–364.

90. Poon D, Anderson BO, Chen LT, et al. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. *Lancet Oncol.* 2009;10:1111–1118.

91. Ministry of Health of the People's Republic of China. Clinical Guidelines of Primary Liver Cancer (2011 version). *Zhonghua Gan Zang Bing Za Zhi.* 2012;20:419–426.

92. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology.* 1999;30:1434–1440.

93. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology.* 1996;111:1018–1022.

94. Capussotti L, Ferrero A, Vigano L, et al. Portal hypertension: contraindication to liver surgery? *World J Surg.* 2006;30:992–999.

95. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology.* 2005;42:1208–1236.

96. Chen XP, Qiu FZ, Wu ZD, et al. Long-term outcome of resection of large hepatocellular carcinoma. *Br J Surg.* 2006;93:600–606.

97. Andreou A, Vauthey JN, Cherqui D, et al. Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy. *J Gastrointest Surg.* 2013;17:66–77discussion 77.

98. Zhang ZM, Guo JX, Zhang ZC, et al. Therapeutic options for intermediate-advanced hepatocellular carcinoma. *World J Gastroenterol.* 2011;17:1685–1689.

99. Abdalla EK, Denys A, Hasegawa K, et al. Treatment of large and advanced hepatocellular carcinoma. *Ann Surg Oncol.* 2008;15:979–985.

100. Ku Y, Iwasaki T, Tominaga M, et al. Reductive surgery plus percutaneous isolated hepatic perfusion for multiple advanced hepatocellular carcinoma. *Ann Surg.* 2004;239:53–60.

101. Wang JH, Lin G, Yan ZP, et al. Stage II surgical resection of hepatocellular carcinoma after TAE:a report of 38 cases. *World J Gastroenterol.* 1998;4:133–136.

102. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet.* 2012;379:1245–1255.

103. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis.* 2005;25:181–200.

104. Torzilli G. Surgical technique: new advancements for expanding indications and safety: the Western experience. *J Hepatobiliary Pancreat Sci.* 2010;17:394–398.

105. Torzilli G, Donadon M, Marconi M, et al. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: results of a prospective analysis. *Arch Surg.* 2008;143:1082–1090.