Original Article

Characteristics and outcomes of hepatocellular carcinoma patients with macrovascular invasion following surgical resection: a meta-analysis of 40 studies and 8,218 patients

Daniel Q. Huang[1,2#], Andrew Tran[3#], Eunice X. Tan[1,2], Sanjna N. Nerurkar[2], Readon Teh[1], Margaret L. P. Teng[1], Ee Jin Yeo[1,4], Biyao Zou[5,6], Connie Wong[7], Carlos O. Esquivel[8], C. Andrew Bonham[8], Mindie H. Nguyen[5,6]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore; [2]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [3]Duke University, Durham, NC, USA; [4]Adelaide Medical School, The University of Adelaide, Adelaide, Australia; [5]Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University Medical Center, Palo Alto, CA, USA; [6]Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA; [7]Lane Medical Library, Stanford University School of Medicine, Stanford, CA, USA; [8]Division of Abdominal Transplantation, Department of Surgery, Stanford University School of Medicine, Stanford, CA, USA

Contributions: (I) Conception and design: DQ Huang, MH Nguyen, A Tran; (II) Administrative support: MH Nguyen; (III) Provision of study materials or patients: DQ Huang, A Tran; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: A Tran, B Zou, DQ Huang, MH Nguyen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Mindie H. Nguyen, MD, MAS, AGAF, FAASLD. Professor of Medicine (Gastroenterology and Hepatology, Liver Transplant) and of Epidemiology and Population Health (by courtesy), Stanford University Medical Center, 780 Welch Road, Palo Alto, CA 94304, USA.
Email: mindiehn@stanford.edu.

Background: Guidelines recommend that hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT) and/or hepatic vein tumor thrombosis (HVTT) should undergo systemic therapy. However, recent data suggest that surgical resection may be beneficial in selected cases, but outcomes are heterogenous. We aimed to estimate pooled overall survival (OS), recurrence free survival (RFS) and complication rates in HCC patients with macrovascular invasion (MVI) following surgical resection.

Methods: In this systematic review and meta-analysis, two investigators independently searched PubMed, Embase, and Cochrane databases from inception to Nov 10, 2020, without language restrictions, for studies reporting outcomes of adult HCC patients with MVI who underwent liver resection with curative intent.

Results: We screened 8,598 articles and included 40 studies involving 8,218 patients. Among all patients with MVI, the pooled median OS was 14.39 months [95% confidence interval (CI): 10.99–18.84], 1-year OS was 54.47% (95% CI: 46.12–62.58%) and 3-year OS was 23.20% (95% CI: 16.61–31.42%). Overall, 1- and 3-year RFS were 27.70% (95% CI: 21.00–35.57%) and 10.06% (95% CI: 6.62–15.01%), respectively. Among patients with PVTT, median OS was 20.41 months in those with segmental/2nd order involvement compared to 12.91 months if 1st order branch was involved and 6.41 months if the main trunk was involved. The pooled rate of major complications was 6.17% (95% CI: 3.53–10.56%).

Conclusions: Overall median survival was 14.39 months for HCC patients with MVI following resection. Median survival was higher in PVTT with segmental/2nd order involvement at 20.41 versus 6.41 months if the main trunk was involved.

Keywords: Hepatocellular carcinoma (HCC); resection; portal vein; macrovascular invasion (MVI); recurrence

Submitted Oct 10, 2021. Accepted for publication Mar 23, 2022.
doi: 10.21037/hbsn-21-419
View this article at: https://dx.doi.org/10.21037/hbsn-21-419

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide (1), with an overall 5-year survival of less than 20% (2). Surgical resection, along with liver transplantation and radiofrequency ablation, are the only curative therapies for HCC (3). However, portal vein tumor thrombosis (PVTT) is present in more than a quarter of cases at the point of diagnosis, while hepatic vein tumor thrombosis (HVTT) is present in around 13% (4-6). These are often considered a contraindication to surgical treatment. As a result, patients with tumor macrovascular invasion (MVI) are classified as Barcelona Clinic Liver Cancer (BCLC) stage C, with treatment options limited to mostly palliative systemic therapy. Prognosis is poor, with untreated patients having a median overall survival (OS) of around 6–8 months and a 1-year survival of 25% (2,7-9).

More recently, data from Asia and the US suggest a survival benefit with surgical resection in well selected HCC patients with MVI (10-12). However, available data are heterogenous likely due in part to the inclusion of patients with tumor thrombus that involved different anatomic levels of the vasculature in different studies. Therefore, the primary purpose of this study was to conduct a systematic review and meta-analysis to evaluate OS, recurrence free survival (RFS) and perioperative complications of HCC patients with MVI who underwent liver resection with curative intent. Our secondary aims were to evaluate the effect of different anatomic sub-classes of MVI on clinical outcomes, as well as to identify factors associated with survival and recurrence. We present the following article in accordance with the PRISMA reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-419/rc).

Methods

In accordance with the PRISMA statement, we conducted and reported the meta-analysis as recommended for meta-analyses of observational studies (Appendix 1) (13).

Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Library databases from inception to Nov 10, 2020 for original full-text research articles, using search terms based on "HCC", "resection", and "survival" as developed in collaboration with a medical librarian (CW) from the Lane Medical Library at Stanford University, CA, USA. Details of the search terms and study selection criteria are available in the Appendix 1. Briefly, we included original research studies published as full-text articles that provided data on adults aged ≥18 years with HCC and portal vein and/or hepatic vein invasion who had undergone primary surgical resection with curative intent and reported OS and/or RFS outcomes. In order to discern the impact of liver resection on survival outcomes of patients with MVI, we excluded studies with patients who received neo-adjuvant therapy for HCC.

Two authors independently searched the databases for relevant articles, screened through them by title and abstract review, followed by a full-text review of potentially eligible articles. Discordance was resolved by consensus or consultation with a third and senior author. Data was extracted from eligible studies using a case report form developed for this study. Quality assessment of included studies was performed using scales developed for this review based on the Newcastle-Ottawa scale (NOS) for retrospective studies (14).

Statistical analysis

We used a random-effects model to determine pooled estimates of demographic and clinical characteristics of HCC patients with MVI. We also used a random-effects model to estimate pooled percentages and 95% confidence intervals (CI) of median, 1-, 3-, and 5-year OS and RFS. We performed pre-planned analyses if there were sufficient data available for the following subgroups: studies that included PVTT only versus PVTT and/or HVTT, sub-classification of PVTT (as recommended by the Liver Cancer Study Group of Japan and the Cheng's classification) (15,16), country/region, alpha-fetoprotein (AFP) levels, number of tumor nodules, tumor histology, status of hepatic function, presence of cirrhosis and etiology of the underlying liver disease. We performed meta-regression to evaluate factors associated with 3- and 5-year OS and RFS for variables with available data such as age, etiology of liver disease, presence of cirrhosis, tumor number, tumor size, sub-classification of MVI, AFP levels and platelet levels.

We assessed for inter-study heterogeneity with the Higgins' and Thompson's I^2 statistics derived from the Cochran's Q test, with heterogeneity considered significant if I^2>50% (17). We utilized the Egger's test and the funnel plot to assess for publication bias. All statistical analyses

© HepatoBiliary Surgery and Nutrition. All rights reserved.

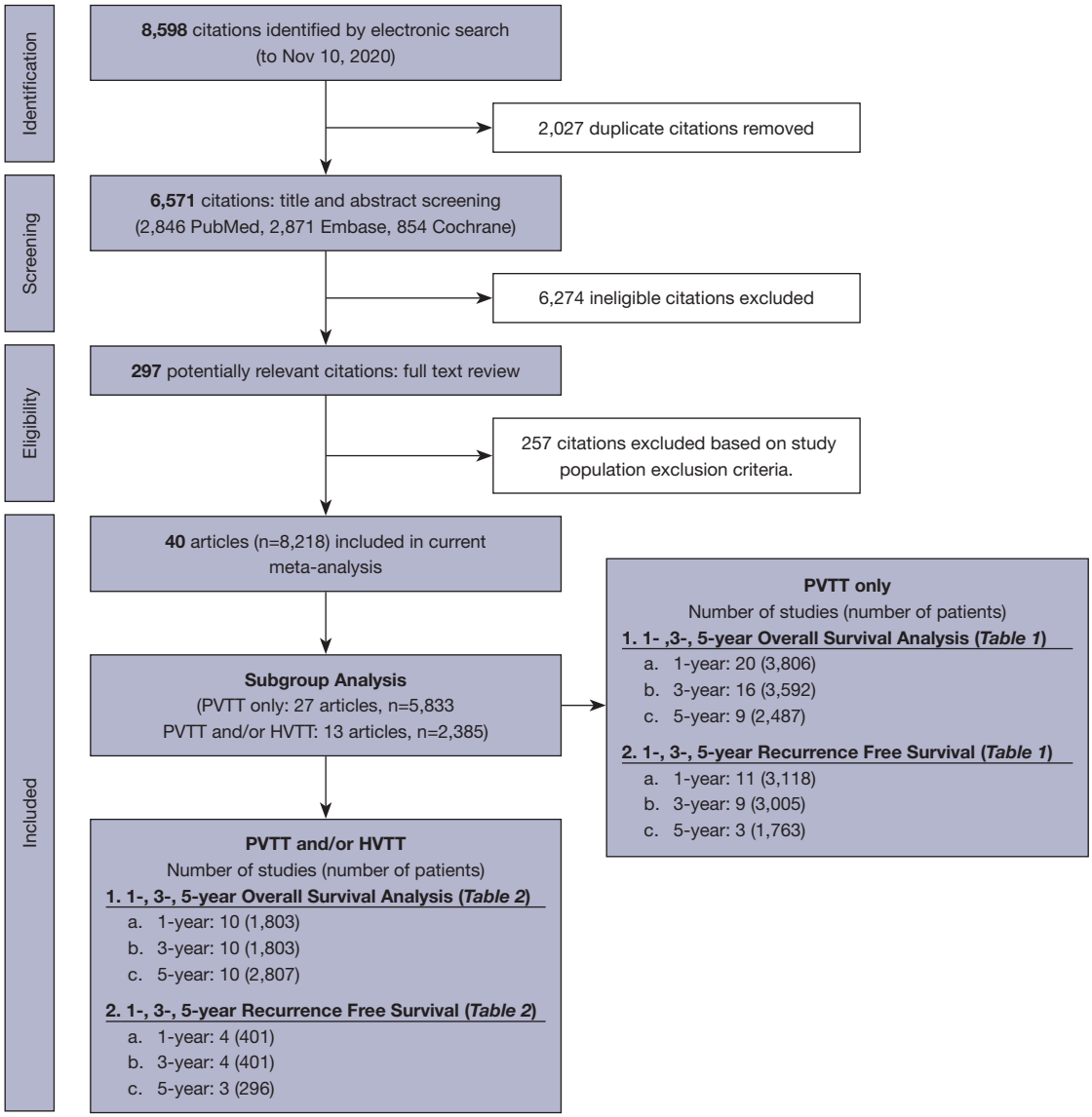

Figure 1 Flow chart of systematic literature search and screening for analysis of HCC resection outcomes in patients with MVI. PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis; HCC, hepatocellular carcinoma; MVI, macrovascular invasion.

were carried out with the meta-packages in R statistical software (version 3.6.1).

Results

Study selection and study characteristics

We screened 8,598 articles, removed 2,027 duplicates, reviewed titles and abstracts of 4,646 articles, identified and reviewed the full text of 297 potentially eligible articles and finally selected 40 studies involving 8,218 patients from 8 countries/regions that met our study inclusion/exclusion criteria (*Figure 1*, *Tables 1*,*2*). Of the included studies, 34 were from Asia, 4 from Europe, 1 from North America and 1 from multiple regions. The study sample size ranged from 12 to 1,517. Details of individual study characteristics are reported in Appendix 1, while each study's patient and tumor characteristics are summarized in Appendix 1. The quality assessment for each study is shown in Appendix 1. Overall, 38 studies were of high quality, 2 studies were of moderate quality, and none were of low quality.

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 1 OS and RFS after liver resection in patients with HCC and only PVTT (not inclusive of patients with HVTT)

Country/region	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P
OS*									
Global	20/3,806	51.77 (40.71–62.65)	–	16/3,592	20.16 (11.52–32.87)	–	9/2,487	21.19 (11.16–36.54)	–
By country/region*									
China	15/3,411	46.68 (34.93–58.81)	<0.0001	12/3,228	15.65 (7.69 – 29.23)	<0.0001	6/2,166	18.25 (8.15 – 35.95)	<0.0001
Japan	1/29	62.10 (43.62–77.63)		1/29	24.10 (11.94–42.65)		1/29	17.20 (7.34–35.27)	
Korea	2/74	72.43* (61.21–81.39)		1/43	42.00 (28.33–57.02)		0/0	–	
Taiwan	1/247	85.00 (79.98–88.93)		1/247	68.00 (61.93–73.52)		1/247	61.00 (54.78–66.89)	
France	1/45	30.80 (19.12–45.60)		1/45	20.50 (11.11–34.71)		1/45	15.40 (7.49–29.03)	
RFS*									
Global	11/3,118	22.67 (16.97–29.60)	–	9/3,005	7.05 (4.99–9.87)	–	3/1,763	0.65 (0.01–26.72)	–
By country*									
China	8/2,999	20.29 (14.27–28.02)	0.15	7/2,917	6.22 (4.39–8.75)	0.04	2/1,718	0.10** (0.00–31.83)	0.12
Korea	2/74	31.17 (19.73–45.48)		1/43	16.00 (7.77–30.09)		0/0	–	
France	1/45	32.50 (20.51–47.33)		1/45	11.60 (5.01–24.63)		1/45	11.60 (5.01–24.63)	

n/n, studies/patients; *, some studies encompassed multiple regions, so they were included in the global analysis but not in the regional/country analysis; **, all I^2>65.2 with P value <0.05, except for values marked. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

Study patient characteristics, overall and by presence of PVTT only or PVTT and/or HVTT

Study and patient characteristics are shown in *Table 3*, and the studies that provided data for these analyses are listed in Appendix 1. Overall, the majority of patients were male (86.80%, 95% CI: 83.39–89.59%), and the pooled mean age was 52.93 years (95% CI: 51.15–54.70) (*Table 3*). More than three-quarter of patients (79.49%, 95% CI: 65.30–88.87%) had cirrhosis, and the pooled mean Model for End-Stage Liver Disease (MELD) score was 7.34 (95% CI: 6.23–8.45). The most common underlying liver disease was hepatitis B virus (HBV) infection (74.37%, 95% CI: 61.77–83.90%), followed by hepatitis C virus (HCV) infection (16.16%, 95% CI: 7.63–31.04%) and alcohol (4.92%, 95% CI: 3.00–7.98%). The pooled mean AFP level was 892.91 ng/mL (496.50–1,289.32) (Appendix 1). With regards to tumor characteristics, the pooled mean tumor size was 7.43 cm (95% CI: 5.44–9.42), the proportion of patients with poorly differentiated HCC was 36.99% (95% CI: 13.08–69.61%), and the proportion with lymphatic invasion was 11.97% (95% CI: 8.48–16.65%) (Appendix 1). The proportion of patients that underwent anatomical resection (6 studies, 517 patients) and non-anatomical resection (5 studies, 493 patients) were 73.60% (95% CI: 44.61–90.61%) and 36.92% (95% CI: 19.14–59.15%) respectively. The pooled

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 2 OS and RFS after liver resection in patients with HCC from studies that included PVTT and/or HVTT

Country/region	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P
OS*									
Global	10/1,803	60.07 (49.22–70.00)	–	10/1,803	27.34 (19.36–37.10)	–	10/2,807	19.78 (13.85–27.44)	–
By country/region*									
China	5/830	54.83 (41.60–67.41)	<0.0001	5/830	17.62** (15.17–20.36)	<0.0001	2/607	11.47* (9.16–14.25)	<0.0001
Japan	1/651	80.00 (76.75–82.90)		1/651	56.60 (52.76–60.36)		2/917	32.42 (19.01–49.51)	
Taiwan	0/0	–		0/0	–		1/76	15.70 (9.12–25.68)	
France	1/26	38.00 (21.73–57.50)		1/26	20.00 (8.73–39.52)		1/26	13.00 (4.55–31.91)	
Italy	1/62	53.30 (49.93–65.27)		1/62	30.10 (20.02–42.56)		1/62	20.00 (11.83–31.78)	
Spain	1/12	66.70 (37.62–86.93)		1/12	33.30 (13.07–62.38)		1/12	22.20 (6.81–52.68)	
United States	0/0	–		0/0	–		1/165	14.00 (9.49–20.17)	
RFS*									
Global	4/401	45.30 (38.00–52.79)	–	4/401	20.88 (11.36–35.22)	–	3/296	17.66 (13.72–22.42)	–
By country*									
China	1/105	51.90 (42.39–61.27)	0.03	1/105	7.90 (4.05–14.84)	0.003	0/0	–	0.59
Italy	1/62	31.70 (21.37–44.21)		1/62	20.80 (12.45–32.66)		1/62	15.60 (8.52–26.85)	
Spain	1/12	58.30 (30.74–81.50)		1/12	43.70 (19.88–70.83)		1/12	21.90 (6.66–52.41)	

n/n, studies/patients; *, some studies encompassed multiple regions, so they were included in the global analysis but not in the regional/country analysis; **, all I^2>89.2, all P value for available I^2 were <0.05. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

median follow-up was 16.60 months (95% CI: 12.35–20.85).

When studies including only PVTT (without HVTT) were compared against studies including PVTT and/or HVTT, the two groups were distinct in terms of age with the former being significantly younger (50.93 years, 95% CI: 49.62–52.24 versus 57.86 years, 95% CI: 52.46–63.27, P=0.01) but similar in terms of gender (P=0.54) and presence of cirrhosis (P=0.56).

OS

Overall analysis (OS)

Overall, 21 studies (3,909 patients) provided data for median OS (Asia 17 studies, 3,611 patients; Europe 3 studies, 133 patients; North America 1 study, 165 patients). The pooled median OS was 14.39 months (95% CI: 10.99–18.84) (*Table 4*). The 1-year (30 studies, 5,609 patients), 3-year

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 3 Study and patient characteristics

Characteristics	Overall		PVTT only		PVTT and/or HVTT		P*
	n/n	Mean/median/% (95% CI)	n/n	Mean/median/% (95% CI)	n/n	Mean/median/% (95% CI)	
Study characteristics							
Median study year	40/8,218	2007	27/5,833	2007	13/2,385	2004	0.21
Median follow-up (months)	9/1,161	16.60 (12.35–20.85)	8/1,133	17.14 (12.66–21.62)	1/28	11.00 (7.70–14.30)	0.06
Patient characteristics							
Male (%)	35/6,128	86.80 (83.39–89.59)	26/4,316	86.99 (82.56–90.42)	9/1,812	85.28 (81.11–88.66)	0.54
Age (years)	31/4,389	52.93 (51.15–54.70)	22/2,953	50.93 (49.62–52.24)	9/1,436	57.86 (52.46–63.27)	0.01
Platelet (10^9/L)	12/2,221	196.60 (174.45–218.75)	8/1,080	195.68 (163.72–227.65)	4/1,141	195.68 (163.72–227.65)	0.94
MELD score	5/928	7.34 (6.23–8.45)	5/928	7.34 (5.93–8.76)	0/0	–	–
Cirrhosis (%)	24/3,930	79.49 (65.30–88.87)	20/3,531	78.30 (60.73–89.39)	4/399	84.51 (64.74–94.19)	0.56
Alcohol (%)	6/890	4.92 (3.00–7.98)	4/428	4.44** (2.85–6.85)	2/462	5.78 (2.65–12.15)	0.56
HBV (%)	29/5,290	74.37 (61.77–83.90)	21/3,454	80.92 (71.73–87.64)	8/1,836	49.75 (19.75–79.93)	0.055
HCV (%)	16/2,622	16.16 (7.63–31.04)	12/1,447	13.84 (5.63–30.19)	4/1,175	41.23 (35.30–47.43)	0.42
Child-Pugh class A (%)	28/5,051	96.21 (93.23–97.91)	21/3,924	93.76 (89.99–96.17)	7/1,127	99.87 (93.85–100.00)	0.051
Child-Pugh class B (%)	27/4,886	4.25 (2.43–7.34)	21/3,924	6.24 (3.83–10.01)	6/962	0.26 (0.01–7.62)	0.07

n/n, studies/patients; *, between PVTT only and PVTT and/or HVTT; **, all I^2>54.6 with P value <0.05, except for values marked; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis; MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

(26 studies, 5,395 patients) and 5-year OS (19 studies, 4,574 patients) were 54.47% (95% CI: 46.12–62.58%), 23.20% (95% CI: 16.61–31.42%) and 20.29% (95% CI: 14.23–28.08%), respectively (*Table 5* and Appendix 1).

Subgroup analyses by presence of PVTT only or PVTT and/or HVTT and by country/region (OS)

Among studies that provided data for PVTT only (without HVTT), median OS was 12.97 months (95% CI: 10.48–16.06) (*Table 4*). The 1-year (20 studies, 3,806 patients), 3-year (16 studies, 3,592 patients) and 5-year OS (9 studies, 2,487 patients) were 51.77% (95% CI: 40.71–62.65%), 20.16% (95% CI: 11.52–32.87%) and 21.19% (95% CI: 11.16–36.54%) (*Table 1*, Appendix 1), respectively.

Among studies that provided data for PVTT and/or HVTT, median OS was 16.83 (95% CI: 10.12–27.98) (*Table 4*). The 1-year (10 studies, 1,803 patients), 3-year (10 studies, 1,803 patients) and 5-year OS (10 studies, 2,807 patients) were 60.07% (95% CI: 49.22–70.00%), 27.34% (95% CI: 19.36–37.10%) and 19.78% (95% CI: 13.85–27.44%), respectively (*Table 2*, Appendix 1). There were no significant differences in 1-, 3- and 5-year OS between the PVTT only group versus the PVTT and/or HVTT only group (all P>0.32).

Country/region level data for OS, where available, are shown in *Tables 1*,*2*,*5*. For OS, most of the studies (n=20) came from China, with other countries contributing 1–2 studies each. The studies included in the analyses of OS are listed in Appendix 1.

Subgroup analyses by sub-classification of PVTT

There were significant differences in the median OS among patients with different levels of vascular invasion. The median OS among patients with segmental/2nd order portal vein branch involvement was 20.41 months (95% CI: 15.16–27.48; 3 studies, 612 patients), versus 12.91 months (95% CI: 9.97–16.72; 3 studies, 466 patients) among patients with 1st order branch involvement and 6.41 months (95% CI: 5.07–8.10; 2 studies, 214 patients) among those with main portal vein trunk/superior mesenteric vein (SMV)

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 4 Median survival, complication rates, operation time and blood loss of liver resection for HCC with MVI

Outcomes and complications	Number of studies	Number of patients	Refer to sub-header
Median survival (months)			
Overall	21	3,909	14.39 (10.99–18.84)
PVTT only	13	2,437	12.97 (10.48–16.06)
PVTT and/or HVTT	8	1,472	16.83 (10.12–27.98)
All complications (%)			
Overall	13	1,698	30.52 (23.60–38.44)
PVTT only	8	1,039	27.37 (19.72–36.63)
PVTT and/or HVTT	5	659	36.59 (24.44–50.72)
Minor complications (%)			
Overall	9	669	24.87 (20.09–30.36)
PVTT only	6	474	21.44 (17.15–26.45)*
PVTT and/or HVTT	3	195	31.79 (25.64–38.66)*
Major complications (%)			
Overall	16	1,687	6.17 (3.53–10.56)
PVTT only	12	1,327	4.86 (2.10–10.82)
PVTT and/or HVTT	4	360	9.17 (6.59–12.61)*
Operation time (min)			
Overall	9	1,253	219.42 (182.77–256.07)
PVTT only	5	749	185.89 (181.06–190.73)
PVTT and/or HVTT	4	504	146.96 (137.32–156.60)
Blood loss (mL)			
Overall	8	1,290	655.76 (434.94–876.58)
PVTT only	6	824	618.28 (342.81–893.75)

*, all I^2>57.4 with P value <0.05, except for values marked. HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

involvement, P<0.0001.

The pooled 1-year OS for segmental and second-order branch involvement, first-order branch involvement and main trunk/SMV involvement were 57.04% (95% CI: 38.92–73.45%), 42.16% (95% CI: 22.71–64.38%) and 19.59% (95% CI: 8.75–38.23%), respectively (*Table 6*).

The pooled 3-year OS for segmental and second-order branch involvement, first-order branch involvement and main trunk/SMV involvement were 28.55% (95% CI: 21.47–36.86%), 17.85% (95% CI: 4.94–47.60%) and 0.00% (95% CI: 0.00–100.00%), respectively (*Table 6* and Appendix 1).

There were insufficient studies reporting 5-year OS for meta-analysis.

RFS

Overall analysis (RFS)

Overall, the 1-year (15 studies, 3,519 patients), 3-year (13 studies, 3,406 patients) and 5-year RFS (6 studies, 2,059 patients) were 27.70% (95% CI: 21.00–35.57%), 10.06% (95% CI: 6.62–15.01%) and 4.31% (95% CI: 0.61–24.76%), respectively (*Table 5*, Appendix 1). The pooled

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 5 OS and RFS after liver resection in patients with HCC and MVI with only PVTT and in those with PVTT and/or HVTT

Country/region	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P
OS*									
Global	30/5,609	54.47 (46.12–62.58)	–	26/5,395	23.20 (16.61–31.42)	–	19/4,574	20.29 (14.23–28.08)	–
By country/region*									
China	20/4,241	48.77 (39.14–58.49)	<0.0001	17/4,058	17.40 (11.26–25.93)	<0.0001	8/2,773	16.13 (8.61–28.16)	<0.0001
Japan	2/680	79.24 (76.02–82.12)		2/680	41.82 (20.97–66.05)		3/946	28.21 (16.64–43.60)	
Korea	2/74	72.43** (61.21–81.39)		1/43	42.00 (28.33–57.02)		0/0	–	
Taiwan	1/247	85.00 (79.98–88.93)		1/247	68.00 (61.93–73.52)		2/323	35.59 (11.01–71.15)	
France	2/71	33.44* (23.48–45.13)		2/71	20.32 (12.51–31.25)		2/71	14.52 (8.07–24.74)	
Italy	1/62	53.30 (40.93–65.27)		1/62	30.10 (20.02–42.56)		1/62	20.00 (11.83–31.78)	
Spain	1/12	66.70 (37.62–86.93)		1/12	33.30 (13.07–62.38)		1/12	22.20 (6.81–52.68)	
United States	0/0	–		0/0	–		1/165	14.00 (9.49–20.17)	
RFS*									
Global	15/3,519	27.70 (21.00–35.57)	–	13/3,406	10.06 (6.62–15.01)	–	6/2,059	4.31 (0.61–24.76)	–
By country*									
China	9/3,104	22.81 (15.45–32.33)	0.002	8/3,022	6.35 (4.63–8.65)	<0.0001	2/1,718	0.10* (0.00–31.83)	0.37
Korea	2/74	31.17 (19.73–45.48)		1/43	16.00 (7.77–30.09)		0/0	–	
France	1/45	32.50 (20.51–47.33)		1/45	11.60 (5.01–24.63)		1/45	11.60 (5.01–24.63)	
Italy	1/62	31.70 (21.37–44.21)		1/62	20.80 (12.45–32.66)		1/62	15.60 (8.52–26.85)	
Spain	1/12	58.30 (30.74–81.50)		1/12	43.70 (19.88–70.83)		1/12	21.90 (6.66–52.41)	

n/n, studies/patients; *, some studies encompassed multiple regions, so they were included in the global analysis but not in the regional/country analysis; **, all I^2>66.0 with P value <0.05, except for values marked. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

proportion of recurrences that were intrahepatic (10 studies, 1,701 patients) and extrahepatic (7 studies, 494 patients) were 56.61% (95% CI: 43.65–68.73%) and 38.75% (95% CI: 16.42–67.07%) respectively.

Among studies that provided data for PVTT only (without HVTT), the 1-year (11 studies, 3,118 patients),

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 6 OS and RFS after liver resection in patients with HCC patients by sub-classification of PVTT

PVTT sub-classification	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P	n/n	Median survival (months) (95% CI)	P
OS												
Segmental & second-order branch[a]	3/396	57.04 (38.92–73.45)	0.02	3/396	28.55 (21.47–36.86)	0.72	1, 20	21.75 (8.77–44.57)	0.98	3, 612	20.41 (15.16–27.48)	<0.0001
First-order branch[b]	4/223	42.16 (22.71–64.38)		3/172	17.85 (4.94–47.60)		1, 21	19.00 (7.31–41.10)		3, 466	12.91 (9.97–16.72)	
Main trunk & SMV[c]	3/101	19.59 (8.75–38.23)		2/70	0.00** (0.00–100.00)		1, 50	0.00 (0.00–100.00)		2, 214	6.41** (5.07–8.10)	
RFS												
Segmental & second-order branch[a]	1/308	16.98 (13.19–21.59)	<0.0001	1/308	5.50 (3.44–8.67)	1.00	0, 0	–	–	–	–	–
First-order branch[b]	2/129	3.67 (2.32–5.76)		1/78	0.00 (0.00–100.00)		0, 0	–		–	–	
Main trunk & SMV[c]	2/51	0.24** (0.01–8.70)		1/20	0.00 (0.00–100.00)		0, 0	–		–	–	

n/n, studies/patients; [a], segmental & second-order branch corresponds to Cheng's classification I and Japan's VP classification VP1 and VP2; [b], first-order branch corresponds to Cheng's classification II and Japan's VP classification VP3; [c], main trunk & SMV corresponds to Cheng's classification III and Japan's VP classification VP4; **, all available I^2>72.9 and all P value for available I^2 were <0.05, except for values marked. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; SMV, superior mesenteric vein.

3-year (9 studies, 3,005 patients) and 5-year RFS (3 studies, 1,763 patients) were 22.67% (95% CI: 16.97–29.60%), 7.05% (95% CI: 4.99–9.87%) and 0.65% (95% CI: 0.01–26.72%), respectively (*Table 1*).

Subgroup analyses by presence of PVTT only or PVTT and/or HVTT and by country/region (RFS)

Among studies that provided data for PVTT and/or HVTT, the 1-year (4 studies, 401 patients), 3-year (4 studies, 401 patients) and 5-year RFS (3 studies, 296 patients) were 45.30% (95% CI: 38.00–52.79%), 20.88% (95% CI: 11.36–35.22%) and 17.66% (95% CI: 13.72–22.42%), respectively (*Table 2*).

There were differences in 1-, 3- and 5-year RFS between the PVTT only (without HVTT) group versus the PVTT and/or HVTT only group (P=0.02 for 1-year, P=0.03 for 3-year, P=0.05 for 5-year).

RFS data, by subclassification of PVTT are shown in *Table 6*.

Country/region level data for RFS, where available, are shown in *Tables 1,2,5*. The studies included in the analyses of RFS are listed in Appendix 1.

Meta-regression of factors associated with survival

Meta-regression of study-level demographic, clinical, and biochemical characteristics for potentially relevant factors with sufficient data did not show any significant association with 5-year OS including age (15 studies, 2,242 patients), cirrhosis (10 studies, 1,237 patients), platelets (7 studies, 1,531 patients), HBV infection (13 studies, 2,441 patients), HCV infection (11 studies, 1,869 patients) or tumor size (8 studies, 1,335 patients) (Appendix 1).

Complications, blood loss and operative time

Overall, pooled complication rates were 30.52% (95% CI: 23.60–38.44%; 13 studies, 1,698 patients) for overall complications and 6.17% (95% CI: 3.53–10.56%; 16 studies, 1,687 patients) for major complications (defined as Clavien-Dindo classification III/IV) (*Table 4*). Subgroup analysis for complication rates in studies reporting outcomes in PVTT only versus PVTT and/or HVTT were similar to the overall analysis (*Table 4*). The pooled operative time and blood loss in the overall analysis was 219.42 (95% CI: 182.77–256.07) min

© HepatoBiliary Surgery and Nutrition. All rights reserved.

and 655.76 (95% CI: 434.94–876.58) mL, respectively.

Additional subgroup analyses

We collected survival data when available for various subgroups (AFP <400 ng/mL, AFP ≥400 ng/mL, presence and absence of cirrhosis, presence of HBV, viral versus non-viral etiology of liver disease, isolated hepatic vein involvement and open versus minimally invasive approaches for surgery). As there were insufficient data to perform meta-analysis, we reported the data in the form of a systematic review in Appendix 1.

Heterogeneity and publication bias

There was moderate heterogeneity among most of the studies (I^2 statistic >54.6%, except for the analysis for alcohol as an etiology of liver disease where heterogeneity was low). The funnel plot (Appendix 1) and Egger's test did not suggest potential publication bias (P=0.13) for 5-year OS.

Discussion

In this systematic review and meta-analysis of 40 studies and 8,218 patients from 8 countries/regions, we determined that HCC patients with MVI who underwent surgical resection with curative intent had a 1- and 3-year OS of 54.5% and 23.2%, respectively. Among studies that reported outcomes for PVTT only (without HVTT), the 1- and 3-year OS were 51.8% and 20.2%, while among studies that reported outcomes for PVTT and/or HVTT, the 1- and 3-year OS were 60.1% and 19.8% respectively. Overall, 1- and 3-year RFS were 27.8% and 10.1%, with similar outcomes in the PVTT only (without HVTT) group (22.7% and 7.1% respectively) and better outcomes in the PVTT and/or HVTT group (45.3% and 20.9%), however, there were limited studies (≤4) that provided RFS data for the PVTT and/or HVTT subgroup and these findings require cautious interpretation. By contrast, a meta-analysis of phase III trials for the treatment of advanced HCC reported a median OS of 10 months for sorafenib; a recent randomized trial demonstrated a median OS of 13 months for lenvatinib and the Imbrave150 trial reported a median OS of 19.2 months with atezolizumab and bevacizumab (18-22). These data suggest that the median survival of resected patients with MVI in general (14 months) may be comparable to that of systemic therapy (2,8), although caution is required in interpreting these data as the current study was not designed to compare outcomes between liver resection and systemic therapy.

Furthermore, in patients with segmental or 2nd order PVTT, median OS was 20.4 months, 1-year OS was 57% and 3-year OS approached 30%, suggesting that surgical resection in this situation may be superior to the multi-kinase inhibitors and comparable to atezolizumab plus bevacizumab. In addition, many patients from countries of lower socioeconomic status do not have access to the newer systemic therapies such as lenvatinib or atezolizumab plus bevacizumab or are unable to afford such costly treatment. Ongoing systemic therapy is often associated with multiple systemic side effects including increased bleeding risk, severe immune associated hepatitis or dermatitis, further complicating the management of these complex patients who are already struggling with poor hepatic reserve and impaired quality of life (23,24). Therefore, surgery may be a viable alternative option in the setting of segmental or 2nd order PVTT (25). Our data is in line with a recent study by Govalan *et al.* (10) which was published after our search was performed. The authors evaluated 11,259 HCC patients with American Joint Commission on Cancer (AJCC) 7th clinical stage TNM (26) $T_{3B}N_0M_0$ and demonstrated that those who underwent resection had a median OS of 21 versus 8 months in those that received systemic therapy. Of note, only 3% of the cohort in the Govalan study received surgery, suggesting that these were highly selected patients, compared with 38% that received systemic therapy. Taken together, these data suggest that a personalized approach should be adopted for HCC patients with MVI, especially those with segmental or 2nd order PVTT, contrary to the latest AJCC 8th edition staging system where any MVI or invasion into adjacent organs are both considered as T4 (27). However, caution must be exercised when interpreting the results, as patients with MVI who underwent liver resection were likely to be highly selected and potentially had fewer comorbidities then those undergoing systemic therapy. In addition, the mean age of patients who underwent resection was only 53 years, younger that the patients included in most clinical trials for systemic therapy (28).

Despite survival being fair in segmental or 2nd order PVTT, 1-year RFS is poor (17%), emphasizing the need for early detection of tumor recurrence in these patients. A study of 734 HCC patients that underwent resection found that lack of tumor surveillance was an independent predictor of mortality (29). We suggest imaging be obtained every 4 months for the first 2 years after surgery, then twice a year thereafter, in line with the National Comprehensive Cancer Network guidelines (30). More data are required

© HepatoBiliary Surgery and Nutrition. All rights reserved.

regarding the use of neo-adjuvant and adjuvant therapy among patients with MVI undergoing resection, given the extremely high recurrence rate.

However, in should be noted that in the setting of tumor involvement of the first order branch or main trunk PV/SMV, the median survival rates were much poorer (12.9 and 6.4 months respectively). Such patients should be considered for systemic therapy rather than invasive surgery.

Regardless of the vascular extent of tumor thrombus and types of therapy, the outcome of patients with advanced HCC is dismal. This highlights the importance of increasing compliance to primary HCC surveillance among patients at risk for HCC, to increase the likelihood of such patients being diagnosed before the development of MVI. Unfortunately, compliance to HCC surveillance has been reported to be very poor in the real world, with most HCC patients diagnosed at a late stage (31-35). A recent nationwide USA study of 82,427 patients with cirrhosis reported that HCC surveillance took place in barely 10% of patients (32). Therefore, there is an urgent need to improve compliance to HCC surveillance and linkage to care (33,36).

In the current study, majority of the included patients (74%) had HBV as the underlying etiology for liver disease, followed by HCV (16%). Although treatment with antivirals has been shown to improve survival and reduce recurrence after HCC treatment (37,38), there is gross under-utilization of anti-viral treatment (37-40). In a multi-center study involving 2,518 patients with HBV-related HCC from the USA and Asia, only 17% of patients were on anti-viral therapy at the time of HCC diagnosis, and only half received HBV anti-viral therapy at any time, highlighting a substantial care gap (38,41) and a significant opportunity for intervention.

We acknowledge the following limitations. There were a lack of data for major underlying liver disease etiologies such as non-alcoholic fatty liver disease (NAFLD) (42) and alcohol-associated liver disease (43), and further studies are needed to examine the outcomes for these populations, especially since the burden of NAFLD and alcohol-associated liver disease are rising. Due to poorer surveillance rates among patients with alcohol-associated liver disease and NAFLD compared with viral-associated liver disease, the proportion of patients with advanced HCC stage and MVI at presentation may increase, therefore, more outcome data for these subgroups are required (35,44). There was marked variation in outcomes among countries/regions, with studies from Taiwan and Japan reporting 1-year OS of around 80% of more, while studies from other countries such as China and France reported 1-year OS of 49% and 33% respectively. However, there were few studies from countries outside of China, and a complete lack of data from South America, Africa and the Middle East. More data are required to accurately determine survival outcomes in these countries. In addition, the outcomes from the sub-classification of PVTT should be interpreted with caution as some of the subgroup analyses only contained a limited number of studies. There were insufficient data among the included studies regarding cases where tumor thrombus crossed the portal vein bifurcation from left to right, or vice versa without entering the main portal vein. More studies are required to evaluate outcomes in this subgroup. The observational nature of the included studies, moderate heterogeneity and the lack of certain data points are further limitations to this study. In addition, this study was not designed to compare the outcomes of surgical resection with systemic therapy, and more data in this area are required.

Conclusions

HCC patients with PVTT and HVTT generally have poor survival after surgical resection, though the median survival is comparable to patients who receive systemic therapy. However, survival is particularly poor if the main portal vein trunk/SMV or 1st order portal vein is involved, suggesting that invasive surgical treatment should be avoided in this setting. On the other hand, more favorable median survival is observed in patients with segmental or 2nd order branch portal vein invasion, suggesting that surgical resection may be a reasonable option in select patients.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-419/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-419/coif). MHN has received research grants from Glycotest, Gilead, B. K. Kee Foundation, and National Cancer Institute; MHN serves on the Advisory Board of Intercept,

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Laboratory of Advanced Medicine, Bayer, Eisai, Gilead, Novartis, Janssen, Eli Lilly, and Exact Sciences. DQH has received a research grant from the National Medical Research Council [Singapore (MOH-000595-01)] and the Exxon-Mobil NUS Scholarship for Clinicians (MOH-000595-01); DQH serves on the Advisory Board of Eisai. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. GLOBOCAN 2020: Global Cancer Observatory. International Agency for Research on Cancer. 2020.
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
3. Koh JH, Tan DJH, Ong Y, et al. Liver resection versus liver transplantation for hepatocellular carcinoma within Milan criteria: a meta-analysis of 18,421 patients. Hepatobiliary Surg Nutr 2022;11:78-93.
4. Cheung TK, Lai CL, Wong BC, et al. Clinical features, biochemical parameters, and virological profiles of patients with hepatocellular carcinoma in Hong Kong. Aliment Pharmacol Ther 2006;24:573-83.
5. Costentin CE, Ferrone CR, Arellano RS, et al. Hepatocellular Carcinoma with Macrovascular Invasion: Defining the Optimal Treatment Strategy. Liver Cancer 2017;6:360-74.
6. Mähringer-Kunz A, Meyer FI, Hahn F, et al. Hepatic vein tumor thrombosis in patients with hepatocellular carcinoma: Prevalence and clinical significance. United European Gastroenterol J 2021;9:590-7.
7. Cabibbo G, Enea M, Attanasio M, et al. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010;51:1274-83.
8. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-80.
9. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-70.
10. Govalan R, Lauzon M, Luu M, et al. Comparison of Surgical Resection and Systemic Treatment for Hepatocellular Carcinoma with Vascular Invasion: National Cancer Database Analysis. Liver Cancer 2021;10:407-18.
11. Kokudo T, Hasegawa K, Matsuyama Y, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65:938-43.
12. Kokudo T, Hasegawa K, Yamamoto S, et al. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. J Hepatol 2014;61:583-8.
13. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PloS Med 2009;6:e1000097.
14. GA Wells, B Shea, D O'Connell, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of andomized ed studies in meta-analyses. 2014.
15. Ikai I, Kudo M, Arii S, et al. Report of the 18th follow-up survey of primary liver cancer in Japan. Hepatol Res 2010;40:1043-59.
16. Shi J, Lai EC, Li N, et al. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011;18:74-80.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
18. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a andomized phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
19. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
20. Finn RS, Qin S, Ikeda M, et al. Imbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol 2021;39:267.
21. Cabibbo G, Cucchetti A, Cammà C, et al. Outcomes of hepatocellular carcinoma patients treated with sorafenib: a meta-analysis of Phase III trials. Future Oncol

© HepatoBiliary Surgery and Nutrition. All rights reserved.

2019;15:3411-22.
22. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
23. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7:6.
24. Sangro B, Chan SL, Meyer T, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72:320-41.
25. Zhang X, Wang J, Shi J, et al. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib for Patients With Unresectable or Metastatic Hepatocellular Carcinoma. JAMA Netw Open 2021;4:e214846.
26. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-4.
27. Kamarajah SK, Frankel TL, Sonnenday C, et al. Critical evaluation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with Hepatocellular Carcinoma (HCC): A Surveillance, Epidemiology, End Results (SEER) analysis. J Surg Oncol 2018;117:644-50.
28. Han Y, Zhi WH, Xu F, et al. Selection of first-line systemic therapies for advanced hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. World J Gastroenterol 2021;27:2415-33.
29. Xu XF, Xing H, Han J, et al. Risk Factors, Patterns, and Outcomes of Late Recurrence After Liver Resection for Hepatocellular Carcinoma: A Multicenter Study From China. JAMA Surg 2019;154:209-17.
30. NCCN. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. 2021.
31. Wolf E, Rich NE, Marrero JA, et al. Use of Hepatocellular Carcinoma Surveillance in Patients With Cirrhosis: A Systematic Review and Meta-Analysis. Hepatology 2021;73:713-25.
32. Yeo YH, Hwang J, Jeong D, et al. Surveillance of patients with cirrhosis remains suboptimal in the United States. J Hepatol 2021;75:856-64.
33. Huang DQ, Yeo YH, Nguyen MH. Letter to the Editor: Hepatocellular Carcinoma Surveillance in Cirrhosis Patients: Is the Real-World Situation Even Worse Than Reported? Hepatology 2021;74:1714-5.
34. Huang DQ, Hoang JK, Leong J, et al. Differential characteristics and outcomes of Asian and non-Asian patients with HBV-related hepatocellular carcinoma. Liver Int 2021;41:1922-32.
35. Chen VL, Yeh ML, Yang JD, et al. Effects of Cirrhosis and Diagnosis Scenario in Metabolic-Associated Fatty Liver Disease-Related Hepatocellular Carcinoma. Hepatol Commun 2020;5:122-32.
36. Huang DQ, Hoang JK, Nguyen MH. HBV-related hepatocellular carcinoma: A call to improve surveillance and linkage to care. Liver Int 2021;41:2238-9.
37. Dang H, Yeo YH, Yasuda S, et al. Cure With Interferon-Free Direct-Acting Antiviral Is Associated With Increased Survival in Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma From Both East and West. Hepatology 2020;71:1910-22.
38. Chen VL, Yeh ML, Le AK, et al. Anti-viral therapy is associated with improved survival but is underutilised in patients with hepatitis B virus-related hepatocellular carcinoma: real-world east and west experience. Aliment Pharmacol Ther 2018;48:44-54.
39. Ogawa E, Yeo YH, Dang N, et al. Diagnosis Rates of Chronic Hepatitis B in Privately Insured Patients in the United States. JAMA Netw Open 2020;3:e201844.
40. Guarino M, Di Costanzo GG, Bruzzese D, et al. Incidence of HCC recurrence after DAA treatment for HCV in a multicentre Italian cohort study. Liver Cancer Int 2020;1:12-24.
41. Huang DQ, Nguyen MH. Treatment eligibility in hepatitis B: a call for better linkage to optimal care. Lancet Gastroenterol Hepatol 2021;6:160.
42. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2021;18:223-38.
43. Global Burden of Disease Liver Cancer Collaboration; Akinyemiju T, Abera S, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683-91.
44. Bucci L, Garuti F, Camelli V, et al. Comparison between alcohol- and hepatitis C virus-related hepatocellular carcinoma: clinical presentation, treatment and outcome. Aliment Pharmacol Ther 2016;43:385-99.

Cite this article as: Huang DQ, Tran A, Tan EX, Nerurkar SN, Teh R, Teng MLP, Yeo EJ, Zou B, Wong C, Esquivel CO, Bonham CA, Nguyen MH. Characteristics and outcomes of hepatocellular carcinoma patients with macrovascular invasion following surgical resection: a meta-analysis of 40 studies and 8,218 patients. HepatoBiliary Surg Nutr 2022;11(6):848-860. doi: 10.21037/hbsn-21-419

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Supplementary

Appendix 1

Search Strategy

PubMed (2846)

((“carcinoma, hepatocellular/surgery"[MeSH Terms] OR "hepatocellular carcinoma"[tw] OR “HCC”[tiab]) AND (resection[tiab] OR "Hepatectomy"[Majr] OR "hepatic lobectomy"[tiab] OR “surgical”[tiab]) AND ("disease-free survival"[Mesh] OR “survival”[tiab] OR recurrence[tiab] OR “neoplasm recurrence, local”[Mesh] OR “disease-free”[tiab]) AND "last 15 years"[dp]) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) AND (“comparative study”[PT] OR “randomized controlled trial”[PT] OR “multicenter study”[PT] OR “retrospective studies”[Mesh] OR “cohort studies”[Mesh] OR “case-control studies”[Mesh] OR “clinical study”[PT] OR “clinical trial”[PT] OR “observational study”[pt])

Cochrane (854)

("hepatocellular carcinoma" OR "hcc") AND (surgery OR surgical OR resection OR lobectomy OR hepatectomy) AND (disease-free OR recurrence OR survival)

Embase: (2871)

(((‘liver cell carcinoma' OR 'hepatocellular carcinoma' OR 'hcc') NEAR/10 (resection OR surgery OR 'hepatic lobectomy' OR 'surgical')) OR ('liver cell carcinoma'/exp/mj AND 'liver resection'/exp/mj)) AND ('disease free survival'/de OR 'disease free interval'/de OR 'cancer survival'/exp OR survival:ti,ab OR recurrence:ti,ab OR 'cancer recurrence'/exp OR 'disease-free':ti,ab) AND human* AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) AND ('article'/it OR 'article in press'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) AND 'surgery'/lnk AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'multicenter study'/de OR 'multicenter study topic'/de OR 'observational study'/de OR 'phase 2 clinical trial topic'/de OR 'phase 3 clinical trial topic'/de OR 'prospective s

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S1 PRISMA

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	–
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5–6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6–7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	*Figure 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplemental *Table 2*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplemental *Table 4*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	*Table 1–4*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	*Table 1–4*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental *Table 4*
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S2 Study characteristics of included studies

Author	Publication year	Study start year	Study end year	Country/region	Study region	Study design	Sample size	Follow-up duration, median/mean (months)
Chen XP[45]	2006	1990	2003	China	Asia	Retrospective	438	–
Peng BG[46]	2009	1996	2004	China	Asia	Retrospective	53	33.6
Fan J[47]	2005	1997	2004	China	Asia	Retrospective	24	–
Shi J[48]	2010	2001	2003	China	Asia	Retrospective	406	6.4
Shi J[16]	2011	2001	2004	China	Asia	Retrospective	441	6.4
Liang LJ[49]	2008	2001	2005	China	Asia	Retrospective	53	10.2
Zheng N[50]	2016	2000	2008	China	Asia	Retrospective	96	60
Peng ZW[51]	2012	2002	2007	China	Asia	Retrospective	201	–
Chen JS[52]	2012	2006	2008	China	Asia	Retrospective	88	–
Cheng YQ[53]	2019	2002	2012	China	Asia	Retrospective	538	–
Tang QH[54]	2013	2006	2008	China	Asia	Retrospective	186	10.7
Li J[55]	2018	2001	2014	China	Asia	Retrospective	169	–
Ye JZ[56]	2014	2007	2009	China	Asia	Retrospective	90	–
Zhang YF[57]	2016	2005	2012	China	Asia	Retrospective	113	15.3
Wang K[58]	2016	2002	2014	China	Asia	Retrospective	745	–
Zhang F[59]	2020	2005	2012	China	Asia	Retrospective	1517	–
Zhang XP[60]	2019	2004	2014	China	Asia	Prospective	432	–
Zhang YF[61]	2015	2006	2013	China	Asia	Retrospective	28	11
Xu JF[62]	2015	2008	2012	China	Asia	Retrospective	56	–
Li J[63]	2016	2009	2013	China	Asia	Retrospective	24	23
Guo WX[64]	2017	2009	2013	China	Asia	Retrospective	45	3
Li N[65]	2016	2010	2013	China	Asia	Prospective	50	8.4
Chen ZH[66]	2019	2012	2016	China	Asia	Retrospective	105	–
Wei X[67]	2019	2016	2017	China	Asia	Retrospective	82	10.8
Matono R[68]	2012	1985	2005	Japan	Asia	Retrospective	29	–
Kokudo T[69]	2017	2000	2007	Japan	Asia	Retrospective	651	–
Hatano E[70]	2018	2000	2010	Japan	Asia	Retrospective	266	–
Lee JM[71]	2016	2000	2011	Korea	Asia	Retrospective	40	–
Lee D[72]	2018	2005	2008	Korea	Asia	Retrospective	43	22
Yu JI[73]	2018	2010	2014	Korea	Asia	Retrospective	31	24.6
Lei HJ[74]	2006	1991	1999	Taiwan	Asia	Prospective	76	–
Liu PH[75]	2014	2002	2012	Taiwan	Asia	Retrospective	247	24
Chok KS[76]	2014	1989	2010	Hong Kong	Asia	Prospective	88	–
Le Treut YP[77]	2006	1988	2004	France	Europe	Retrospective	26	–
Pesi B[78]	2015	1987	2009	Italy	Europe	Retrospective	62	82.8
Roayaie S[79]	2013	1992	2010	USA	North America	Prospective	165	11.9
Lim C[80]	2015	1995	2012	France	Europe	Retrospective	45	17.5
Cortese S[81]	2020	2007	2015	Spain	Europe	Retrospective	12	81.3
Torzilli G[82]	2013	1990	2009	Multicenter	Multicenter	Retrospective	297	–
Ye J[83]	2016	2009	2011	China	Asia	Retrospective	160	–

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S3 Patient and tumor characteristics of included studies

Author	Publication year	Overall number of pts with PVTT	Overall number of pts with HVTT	Mean age - years (SD)	Male (%)	Cirrhosis (%)	Mean platelet (SD) (x 10^9/L)	Size - cm (SD)	Number of nodules (SD)	Single tumour (%)	Multiple nodules (%)	Mean MELD (SD)	Mean AFP (SD)	Poorly differentiated histology (%)	Follow-up duration, median/ mean (months)
Chen XP[45]	2006	438	–	–	87	–	–	–	–	83	17	–	–	–	–
Peng BG[46]	2009	53	–	50.2 (7.5)	94	70	–	8.39 (2.29)	–	–	–	–	–	–	33.6
Fan J[47]	2005	24	-	–	83	–	–	–	–	58	42	–	–	–	–
Shi J[48]	2010	406	–	47.3 (10)	89	79	146.5 (72.8)	–	–	–	–	–	710.2 (417.9)	–	6.4
Shi J[16]	2011	441	–	–	90	–	–	–	–	91	9	–	–	–	6.4
Liang LJ[49]	2008	53	–	46.41 (10.21)	91	77	–	–	–	62	38	–	–	–	10.2
Zheng N[50]	2016	96	–	51.9 (48.2)	78	100	–	7.9 (2.2)	2.4 (1.4)	–	–	7.1 (1.4)	1120.6 (3930.7)	–	60
Peng ZW[51]	2012	201	–	–	93	88	–	–	–	47	53	–	–	–	–
Chen JS[52]	2012	88	–	48.2 (11.4)	93	83	202.4 (78.4)	10.1 (3.5)	–	51	49	–	–	–	–
Cheng YQ[53]	2019	538	–	–	92	70	–	–	–	93	7	–	–	–	–
Tang QH[54]	2013	186	–	48.4 (9.1)	89	80	–	9.53 (3.43)	–	54	46	–	–	–	10.7
Li J[55]	2018	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ye JZ[56]	2014	–	–	49.3 (10.7)	90	–	–	6.9 (1.6)	–	57	43	–	–	–	–
Zhang YF[57]	2016	113	–	49 (11.2)	88	42	209.1 (83.6)	8.5 (4.1)	–	85	15	4.6 (3.1)	–	–	15.3
Wang K[58]	2016	745	–	–	91	69	–	–	–	93	7	–	–	–	–
Zhang F[59]	2020	1517	–	–	–	–	–	–	–	–	–	–	–	–	–
Zhang XP[60]	2019	432	–	–	91	70	–	–	–	87	13	8.82 (3.94)	–	–	–
Zhang YF[61]	2015	–	–	47.4 (10.3)	96	96	208.6 (77.3)	9.6 (3.4)	–	61	39	–	–	–	11
Xu JF[62]	2015	56	–	–	20	61	–	5.6 (4.5)	–	34	66	–	–	–	–
Li J[63]	2016	24	–	52.8 (6.9)	100	100	164.3 (48.6)	–	–	–	–	–	–	17	23
Guo WX[64]	2017	45	–	50.1 (9.2)	89	82	–	9.4 (2.3)	–	–	–	–	–	–	3
Li N[65]	2016	50	–	–	84	60	–	–	–	80	20	–	–	10	8.4
Chen ZH[66]	2019	37	105	–	90	–	–	–	–	80	20	–	–	–	–
Wei X[67]	2019	82	–	50.5 (10.1)	90	17	–	–	–	84	16	–	–	90	10.8
Matono R[68]	2012	29	–	–	86	–	–	–	–	–	–	–	–	–	–
Kokudo T[69]	2017	420	546	64 (11)	83	–	190 (86.9)	8.78 (5.13)	–	–	–	–	–	–	–
Hatano E[70]	2018	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lee JM[71]	2016	40	–	55 (12.9)	75	68	-	–	–	–	–	8.3 (3.0)	10728 (25073)	–	–
Lee D[72]	2018	43	–	–	84	–	–	–	–	53	47	–	–	–	22
Yu JI[73]	2018	31	–	–	81	45	–	–	–	81	19	–	–	–	24.6
Lei HJ[74]	2006	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Liu PH[75]	2014	247	–	58 (14)	82	100	–	–	–	66	34	7.9 (2.1)	13130 (46071)	–	24
Chok KS[76]	2014	88	–	–	95	–	–	–	–	–	–	–	–	32	–
Le Treut YP[77]	2006	–	–	–	85	–	–	–	–	–	–	–	–	–	–
Pesi B[78]	2015	41	11	–	–	90	–	–	–	–	–	–	–	–	82.8
Roayaie S[79]	2013	–	–	55.8 (11.8)	80	–	214 (102)	0.9 (0.559)	1.4 (0.8)	–	–	–	21840 (76548)	42	11.9
Lim C[80]	2015	45	–	57 (12)	73	16	276.5 (130.9)	1.64 (0.483)	1.5 (1.1)	–	–	–	500 (–)	–	17.5
Cortese S[81]	2020	11	1	59.8 (11.8)	83	92	–	–	1.5 (0.8)	–	–	–	1349.6 (642.9)	–	81.3
Torzilli G[82]	2013	–	–	–	77	57	–	–	–	–	–	–	–	–	–
Ye J[83]	2016	160	–	52.17 (21.09)	76	–	251.11 (73.56)	–	–	–	–	–	–	–	–

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S4 Quality assessment of included studies (NOS)

Author	Publication year	Study starty year	Study end year	Representativeness (0,1,2)	HCC as outcome of interest (0,1,2)	Sample size (0,1)	Comparability of study population (0,2)	Outcome assessment (0,1)	Statistical test (0,1)	Total Score (0-9)
Chen XP[45]	2006	1990	2003	2	2	1	2	1	1	9
Peng BG[46]	2009	1996	2004	2	2	1	2	1	1	9
Fan J[47]	2005	1997	2004	2	2	0	2	1	1	8
Shi J[48]	2010	2001	2003	2	2	1	2	1	1	9
Shi J[16]	2011	2001	2004	2	2	1	2	1	1	9
Liang LJ[49]	2008	2001	2005	2	2	1	2	1	1	9
Zheng N[50]	2016	2000	2008	2	2	1	2	1	1	9
Peng ZW[51]	2012	2002	2007	2	2	1	2	1	1	9
Chen JS[52]	2012	2006	2008	2	2	1	2	1	1	9
Cheng YQ[53]	2019	2002	2012	2	2	1	2	1	1	9
Tang QH[54]	2013	2006	2008	2	2	1	2	1	1	9
Li J[55]	2018	2001	2014	2	2	1	2	1	1	9
Ye JZ[56]	2014	2007	2009	2	2	1	2	1	1	9
Zhang YF[57]	2016	2005	2012	2	2	1	2	1	1	9
Wang K[58]	2016	2002	2014	2	2	1	2	1	1	9
Zhang F[59]	2020	2005	2012	2	2	1	2	1	1	9
Zhang XP[60]	2019	2004	2014	2	2	1	2	1	1	9
Zhang YF[61]	2015	2006	2013	2	2	0	2	1	1	8
Xu JF[62]	2015	2008	2012	2	2	1	2	1	1	9
Li J[63]	2016	2009	2013	1	2	0	0	1	1	5
Guo WX[64]	2017	2009	2013	2	2	0	2	1	1	8
Li N[65]	2016	2010	2013	2	2	1	2	1	1	9
Chen ZH[66]	2019	2012	2016	2	2	1	2	1	1	9
Wei X[67]	2019	2016	2017	1	2	1	2	1	1	8
Matono R[68]	2012	1985	2005	1	2	0	0	1	1	5
Kokudo T[69]	2017	2000	2007	1	2	1	2	1	1	8
Hatano E[70]	2018	2000	2010	1	2	1	2	1	1	8
Lee JM[71]	2016	2000	2011	2	2	0	2	1	1	8
Lee D[72]	2018	2005	2008	2	2	0	2	1	1	8
Yu JI[73]	2018	2010	2014	2	2	0	2	1	1	8
Lei HJ[74]	2006	1991	1999	2	2	1	2	1	1	9
Liu PH[75]	2014	2002	2012	2	2	1	2	1	1	9
Chok KS[76]	2014	1989	2010	2	2	1	2	1	1	9
Le Treut YP[77]	2006	1988	2004	2	2	0	2	1	1	8
Pesi B[78]	2015	1987	2009	2	2	1	2	1	1	9
Roayaie S[79]	2013	1992	2010	2	2	1	2	1	1	9
Lim C[80]	2015	1995	2012	2	1	0	2	1	1	8
Cortese S[81]	2020	2007	2015	2	2	0	2	1	1	8
Torzilli G[82]	2013	1990	2009	2	2	1	2	1	1	9
Ye J[83]	2016	2009	2011	2	2	1	2	1	1	9

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S5 Studies* that provided data for study, patient and tumour characteristics, by the presence of only portal vein tumor thrombosis (PVTT) or with PVTT and/or hepatic vein tumor thrombosis (HVTT).

	Overall		PVTT Only		PVTT and/or HVTT	
	Number of Studies	Study reference number	Number of Studies	Study reference number	Number of Studies	Study reference number
Study Characteristics						
Median study year	40	16, 45-83	27	16 46 47 48 49 50 51 52 53 54 57 58 59 60 62 63 64 65 67 68 71 72 73 75 76 80 83	13	45 55 56 61 66 69 70 74 77 78 79 81 82
Median follow up (months)	9	16 46 54 61 65 67 72 73 75	8	16 46 54 65 67 72 73 75	1	61
Patient Characteristics						
Male (%)	35	16 45 46 47 48 49 50 51 52 53 54 56 57 58 60 61 62 63 64 65 66 67 68 69 71 72 73 75 76 77 79 80 81 82 83	26	16 46 47 48 49 50 51 52 53 54 57 58 60 62 63 64 65 67 68 71 72 73 75 76 80 83	9	45 56 61 66 69 77 79 81 82
Age (Years)	31	16 46 48 49 50 51 52 54 56 57 60 61 63 64 65 66 67 68 69 71 72 73 75 76 77 78 79 80 81 82 83	22	16 46 48 49 50 51 52 54 57 60 63 64 65 67 68 71 72 73 75 76 80 83	9	56 61 66 69 77 78 79 81 82
Platelet (10^9/L)	12	48 51 52 57 61 63 69 72 79 80 82 83	8	48 51 52 57 63 72 80 83	4	61 69 79 82
MELD Score	5	50 57 60 71 75	5	50 57 60 71 75	0	
Cirrhosis (%)	24	46 48 49 50 51 52 53 54 57 58 60 61 62 63 64 65 67 71 73 75 78 80 81 82	20	46 48 49 50 51 52 53 54 57 58 60 62 63 64 65 67 71 73 75 80	4	61 78 81 82
Alcohol (%)	6	50 71 75 79 80 82	4	50 71 75 80	2	79 82
HBV (%)	29	16 45 46 48 49 50 52 53 54 56 57 58 61 62 63 65 66 67 68 69 71 72 73 75 76 78 79 80 82	21	16 46 48 49 50 52 53 54 57 58 62 63 65 67 68 71 72 73 75 76 80	8	45 56 61 66 69 78 79 82
HCV (%)	16	46 48 52 50 55 52 54 57 62 68 69 71 75 76 78 79 80 82	12	46 48 50 52 54 57 62 68 71 75 76 80	4	69 78 79 82
Child-Pugh A (%)	28	16 46 47 48 49 50 51 52 53 54 56 58 60 61 62 63 65 66 67 69 71 72 73 75 76 77 78 79	21	16 46 47 48 49 50 51 52 53 54 58 60 62 63 65 67 71 72 73 75 76	7	56 61 66 69 77 78 79
Child-Pugh B (%)	27	16 46 47 48 49 50 51 52 53 54 56 58 60 61 62 63 65 66 67 69 71 72 73 75 76 77 78	21	16 46 47 48 49 50 51 52 53 54 58 60 62 63 65 67 71 72 73 75 76	6	56 61 66 69 77 78

*References are listed in the supplemental reference list.

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S6 Overall tumor and liver function characteristicsa.

Characteristics	N (n) (n)[b]	Mean / Median / % (95% CI)
Tumor number	5 (540)	1.58 (1.14 – 2.01)
Tumor size (cm)	14 (1,747)	7.43 (5.44 – 9.42)
Poorly differentiated histology (%)	5 (409)	36.99 (13.08 – 69.61)
Lymphatic invasion	3 (803)	11.97 (8.48 – 16.65)
Alpha-fetoprotein (ng/mL)	11 (1,336)	892.91 (496.50 – 1289.32)
Child-Pugh A (%)	28 (5,051)	96.21 (93.23 – 97.91)
Child-Pugh B (%)	27 (4,886)	4.25 (2.43 – 7.34)

[a], All I^2>87.3, all P value for available I^2 were <0.05; [b], N, number of studies; n, number of patients

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S7A Studies* that provided data for overall survival (A) and recurrence free survival (B) after liver resection in patients with hepatocellular carcinoma with only portal vein tumor thrombosis (PVTT) or with PVTT and/or hepatic vein tumor thrombosis.

Region	Number of Studies	Reference numbers of studies that provided data for 1-year (%)	Number of Studies	Reference numbers of studies that provided data for 3-year (%)	Number of Studies	Reference numbers of studies that provided data for 5-year (%)
Overall Survival						
Overall	30	16 45 46 47 48 49 50 51 52 54 55 56 57 59 61 62 64 65 66 67 68 69 72 73 75 77 78 80 81 82	26	16 45 46 47 48 49 50 51 52 54 55 56 57 59 61 65 66 68 69 72 75 77 78 80 81 82	19	45 46 50 51 54 55 57 59 68 69 70 74 75 77 78 79 80 81 82
By Country/region						
China	20	16 45 46 47 48 49 50 51 52 54 55 56 57 59 61 62 64 65 66 67	17	16 45 46 47 48 49 50 51 52 54 55 56 57 59 61 65 66	8	45 46 50 51 54 55 57 59
Japan	2	68 69	2	68 69	3	68 69 70
Korea	2	72 73	1	72	0	--
Taiwan	1	75	1	75	2	74 75
France	2	77 80	2	77 80	2	77 80
Italy	1	78	1	78	1	78
Spain	1	81	1	81	1	81
United States	0	–	0	–	1	79
Recurrence-Free Survival						
Overall	15	16 48 49 51 54 57 59 66 67 72 73 78 80 81 82	13	16 48 49 51 54 57 59 66 72 78 80 81 82	6	51 59 78 80 81 82
By Country						
China	9	16 48 49 51 54 57 59 66 67	8	16 48 49 51 54 57 59 66	2	51 59
Korea	2	72 73	1	72	0	–
France	1	80	1	80	1	80
Italy	1	78	1	78	1	78
Spain	1	81	1	81	1	81

*References are listed in the supplemental reference list.

Table S7B Studies* that provided data for overall survival (A) and recurrence free survival (B) after liver resection in patients with hepatocellular carcinoma and only portal vein tumor thrombosis (not inclusive of patients with hepatic vein tumor thrombus) .

Region	Number of Studies	Reference numbers of studies that provided data for 1-year (%)	Number of Studies	Reference numbers of studies that provided data for 3-year (%)	Number of Studies	Reference numbers of studies that provided data for 5-year (%)
Overall Survival						
Overall	20	16 46 47 48 49 50 51 52 54 57 59 62 64 65 67 68 72 73 75 80	16	16 46 47 48 49 50 51 52 54 57 59 65 68 72 75 80	9	46 50 51 54 57 59 68 75 80
By Country/region						
China	15	16 46 47 48 49 50 51 52 54 57 59 62 64 65 67	12	16 46 47 48 49 50 51 52 54 57 59 65	6	46 50 51 54 57 59
Japan	1	68	1	68	1	68
Korea	2	72 73	1	72	0	--
Taiwan	1	75	1	75	1	75
France	1	80	1	80	1	80
Recurrence-Free Survival						
Overall	11	16 48 49 51 54 57 59 67 72 73 80	9	16 48 49 51 54 57 59 72 80	3	51 59 80
By Country						
China	8	16 48 49 51 54 57 59 67	7	16 48 49 51 54 57 59	2	51 59
Korea	2	72 73	1	72	0	--
France	1	80	1	80	1	80

*References are listed in the supplemental reference list.

Table S7C Studies* that provided data for overall survival (A) and recurrence free survival (B) after liver resection in patients with hepatocellular carcinoma with hepatocellular carcinoma with portal vein tumor thrombosis and/or hepatic vein tumor thrombosis.

Region	Number of Studies	Reference numbers of studies that provided data for 1-year (%)	Number of Studies	Reference numbers of studies that provided data for 3-year (%)	Number of Studies	Reference numbers of studies that provided data for 5-year (%)
Overall Survival						
Overall	10	45 55 56 61 66 69 77 78 81 82	10	45 55 56 61 66 69 77 78 81 82	10	45 55 69 70 74 77 78 79 81 82
By Country/region						
China	5	45 55 56 61 66	5	45 55 56 61 66	2	
Japan	1	69	1	69	1	69
Taiwan	0	--	0	--	1	74
France	1	77	1	77	1	77
Italy	1	78	1	78	1	78
Spain	1	81	1	81	1	81
United States	0	--	0	--	1	79
Recurrence-Free Survival						
Overall	4	66 78 81 82	4	66 78 81 82	3	78 81 82
By Country						
China	1	66	1	66	0	--
Italy	1	78	1	78	1	78
Spain	1	81	1	81	1	81

*References are listed in the supplemental reference list.

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S8 Studies that provided data for overall survival (A) and recurrence free survival (B) after liver resection in patients with hepatocellular carcinoma by presence of and sub-classification of portal vein tumor thrombosis.

Sub-classification	Number of Studies	Reference numbers of studies that provided data for 1-year (%)	Number of Studies	Reference numbers of studies that provided data for 3-year (%)	Number of Studies	Reference numbers of studies that provided data for 5-year (%)	Number of Studies	Reference numbers of studies that provided data for Median Survival
Overall Survival								
Segmental & Second-Order Branch	3	48 78 83	3	48 78 83	1	78	3	48 58 83
First-Order Branch	4	48 67 78 83	3	48 78 83	1	78	3	48 58 83
Main Trunk & Superior Mesenteric Vein	3	48 65 67	2	48 65	1	65	2	48 58
Recurrence-Free Survival								
Segmental & Second-Order Branch	1	48	1	48	0	–	0	–
First-Order Branch	2	48	1	48	0	–	0	–
Main Trunk & Superior Mesenteric Vein [c]	2	48 67	1	48	0	–	0	–

*References are listed in the supplemental reference list.

Table S9 Meta-regression of variables associated with 5-year overall survival after surgical resection

Characteristics	N (n)[a]	Coefficient	95% CI	P
Age, per year	15 (2,242)	0.0213	-0.0591 – 0.1016	0.6037
Tumor size, cm	8 (1,335)	0.1056	-0.0373 – 0.2486	0.1475
Cirrhosis	10 (1,237)	0.0027	-0.0038 – 0.0092	0.4168
Platelet (per 10^9 increase)	7 (1,531)	0.0045	-0.0121 – 0.0211	0.5944
Hepatitis B	13 (2,441)	-0.0011	-0.0080 – 0.0059	0.7638
Hepatitis C	11 (1,869)	0.0027	-0.0032 – 0.0085	0.3711

[a], N, number of studies; n, number of patients

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S10 Systematic review of overall survival (OS) after liver resection in patients with hepatocellular carcinoma and macrovascular invasion, by tumor characteristics and characteristics of liver disease

Variable	Study author	Number of patients[a]	Median survival (months) (95% CI)	1-year OS (%)	3-year OS (%)	5-year OS (%)
Tumor characteristics						
AFP < 400	Chen JS[52]	32	10			
AFP ≥ 400	Chen JS[52]	56	8			
Characteristics of liver disease						
Non-Cirrhosis	Chen JS[52]	15	9			
	Pesi B[78]	6		50	16.6	0
Cirrhosis	Chen JS[52]	73	9			
	Li J[63]	24	30 (24.1 – 36.0)			
Hepatitis B virus	Shi J[48]	354	14.1			
	Chen JS[52]	79	9			
	Li J[63]	24	30 (24.1 – 36.0)			

[a], Number of patients within the specified subgroup

Table S11 Systematic review of overall survival (OS) and recurrence-free survival (RFS) after liver resection in patients with hepatocellular carcinoma and macrovascular invasion, by viral versus non-viral etiology.

Study author	Median OS (months) (95% CI)	1-year OS (%)	3-year OS (%)	5-year OS (%)	1-year RFS (%)	3-year RFS (%)	5-year RFS (%)
Viral							
Cheng YQ[53]	9.2	–	–	–	–	–	–
Pesi B[78]	–	57.10	34.80	21.70	–	–	–
Torzilli G[82]	–	85	58	53	51	36	30
Non-Viral							
Cheng YQ[53]	16.0	–	–	–	–	–	–
Pesi B[78]	–	47.50	25.30	25.30	–	–	–
Torzilli G[82]	–	77	53	0	52	0	0

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Table S12 Systematic review of overall survival (OS) and recurrence-free survival (RFS) after liver resection in patients with hepatocellular carcinoma and macrovascular invasion for isolated hepatic vein tumor thrombosis (HVTT).

Study author	Number of patients[†]	Median OS (months) (95% CI)	1-year OS (%)	3-year OS (%)	5-year OS (%)	Median RFS (months) (95% CI)
Peripheral hepatic vein tumor thrombosis						
Chen ZH[66]	21	–	–	–	–	–
Kokudo T[69]	305	58.20	–	–	–	28.32
Major hepatic vein tumor thrombosis						
Chen ZH[66]	10	–	–	–	–	–
Kokudo T[69]	170	56.04	–	–	–	10.56
Pesi B[78]	8	–	75	45	31	–
Cortese S[81]	1	–	–	–	–	–
Tumor thrombosis of the inferior vena cava						
Chen ZH[66]	74	–	52.70	14.86	–	–
Kokudo T[69]	71	16.44	–	–	–	9.84
Pesi B[78]	3	–	50	0	0	–

[†], Number of patients within the specified subgroup

Table S13 Median overall survival (OS), overall survival, and recurrence-free survival (RFS) after liver resection in patients with hepatocellular carcinoma and macrovascular invasion by surgery type.

Study author	Median OS (months) (95% CI)	1-year OS (%)	3-year OS (%)	5-year OS (%)	1-year RFS (%)	3-year RFS (%)	5-year RFS (%)
Open surgery (%)							
Zhang F[59]	21	67	30	10	57	21	4
Chen ZH[66]	19.4	64.2	19.7	–	51.9	22.6	–
Lim C[80]	4.8	30.8	20.5	15.4	32.5	11.6	11.6
Minimally invasive surgery (%)							
Pesi B[78]	12.9	53.30	30.10	20.00	31.70	20.80	15.60

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

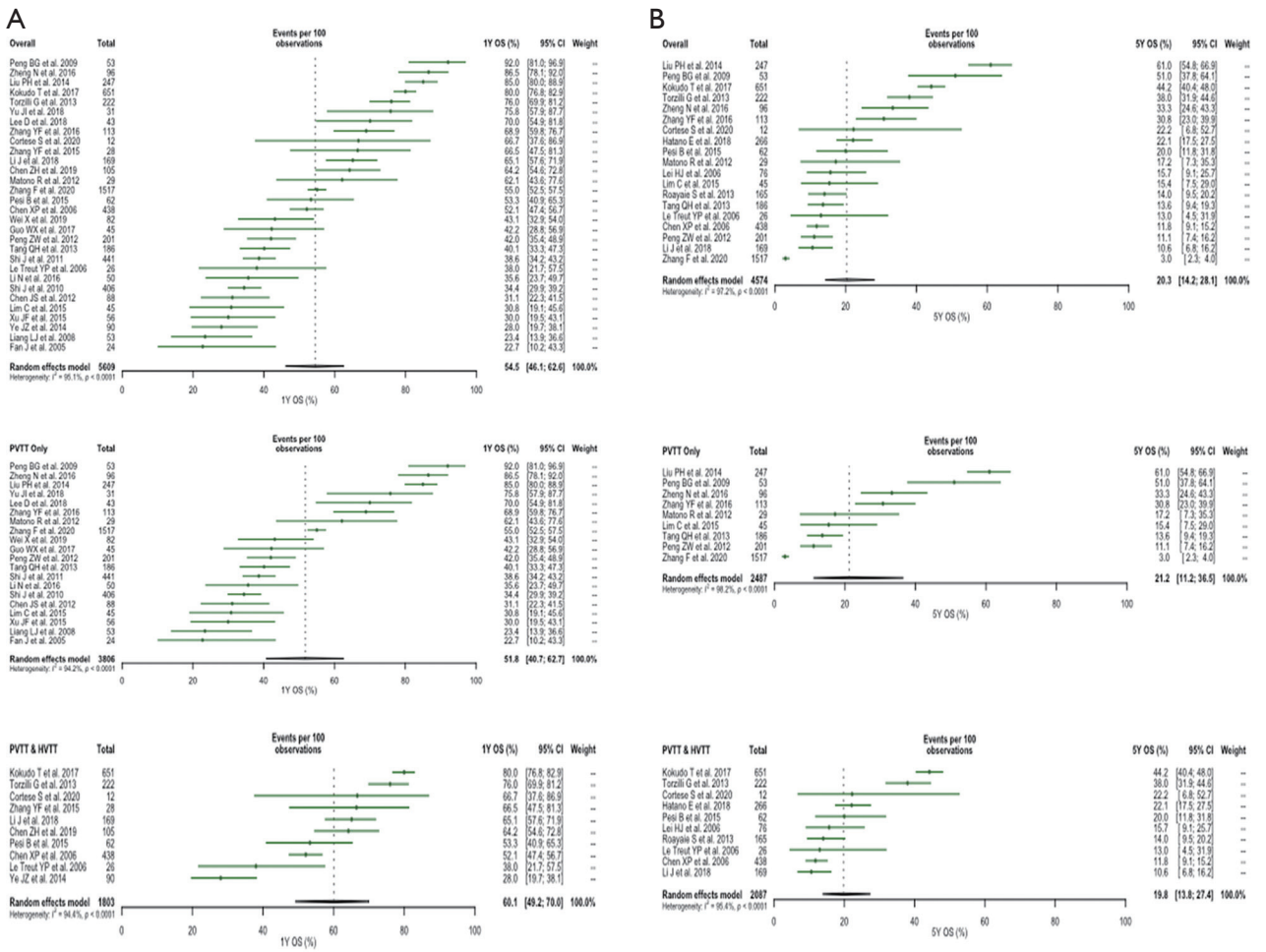

Figure S1 Overall survival. (A) Forest plot for 1-year overall survival, overall and by the presence of only PVTT or with PVTT and/or HVTT. (B) Forest plot for 5-year overall survival overall and by the presence of only PVTT or with PVTT and/or HVTT. PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

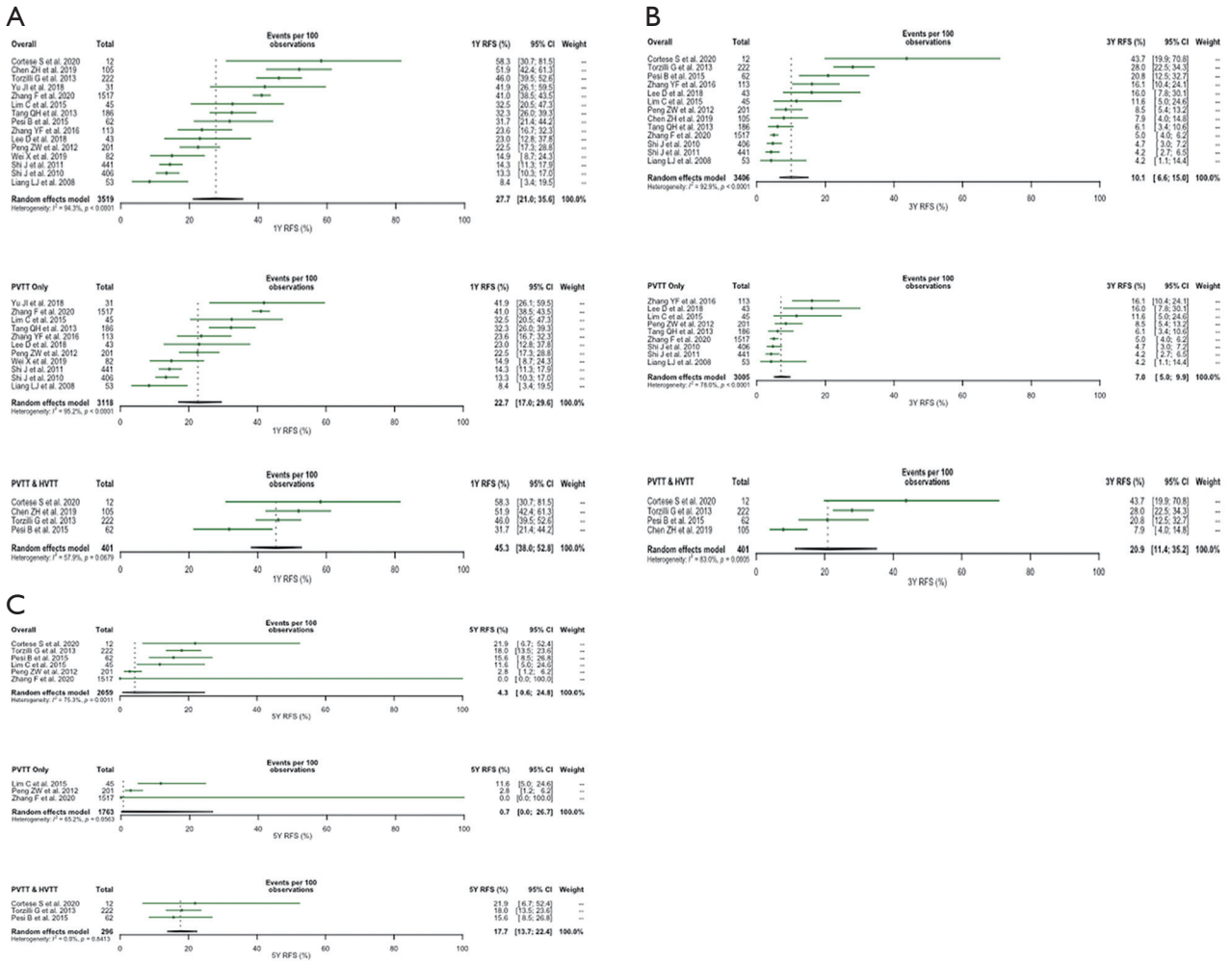

Figure S2 Recurrence free survival. (A) Forest plot for 1-year recurrence free survival overall and by the presence of only PVTT or with PVTT and/or HVTT. (B) Forest plot for 3-year recurrence free survival overall and by the presence of only PVTT or with PVTT and/or HVTT. (C) Forest plot for 5-year recurrence-free survival overall and by the presence of only PVTT or with PVTT and/or HVTT. PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

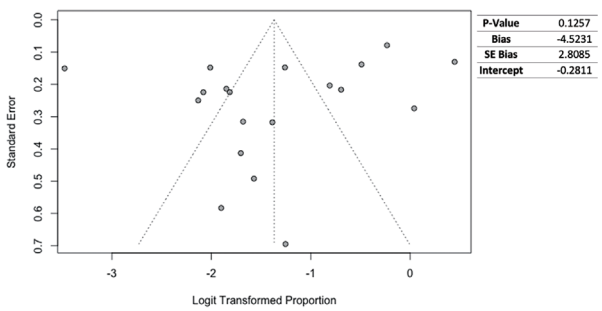

Figure S3 Egger's test and funnel plot for 5-year overall survival.

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

References

45. 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;13:940-6.
46. Peng BG, He Q, Li JP, et al. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg 2009;198:313-8.
47. 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;11:1215-9.
48. Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol 2010;17:2073-80.
49. 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;32:627-31.
50. Zheng N, Wei X, Zhang D, et al. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. Medicine (Baltimore) 2016;95:e3959.
51. 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;118:4725-36.
52. 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;175:243-50.
53. Cheng YQ, Wang K, Zhang XP, et al. Thrombocytopenia: A prognostic factor for hepatocellular carcinoma patients with portal vein tumor thrombus after hepatectomy. J Gastroenterol Hepatol 2019;34:1214-21.
54. 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;37:1362-70.
55. Li J, Huang L, Yan J, et al. Liver resection for hepatocellular carcinoma: personal experiences in a series of 1330 consecutive cases in China. ANZ J Surg 2018;88:E713-7.
56. Ye JZ, Zhang YQ, Ye HH, et al. Appropriate treatment strategies improve survival of hepatocellular carcinoma patients with portal vein tumor thrombus. World J Gastroenterol 2014;20:17141-7.
57. Zhang YF, Le Y, Wei W, et al. Optimal surgical strategy for hepatocellular carcinoma with portal vein tumor thrombus: a propensity score analysis. Oncotarget 2016;7:38845-56.
58. Wang K, Guo WX, Chen MS, et al. Multimodality Treatment for Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Large-Scale, Multicenter, Propensity Mathching Score Analysis. Medicine (Baltimore) 2016;95:e3015.
59. Zhang F, Lu CD, Zhang XP, et al. The impact of portal vein tumor thrombus on long-term survival after liver resection for primary hepatic malignancy. HPB (Oxford) 2020;22:1025-33.
60. Zhang XP, Gao YZ, Chen ZH, et al. An Eastern Hepatobiliary Surgery Hospital/Portal Vein Tumor Thrombus Scoring System as an Aid to Decision Making on Hepatectomy for Hepatocellular Carcinoma Patients With Portal Vein Tumor Thrombus: A Multicenter Study. Hepatology 2019;69:2076-90.
61. Zhang YF, Wei W, Guo ZX, et al. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with hepatic vein tumor thrombus. Jpn J Clin Oncol 2015;45:837-43.
62. Xu JF, Liu XY, Wang S, et al. Surgical treatment for hepatocellular carcinoma with portal vein tumor thrombus: a novel classification. World J Surg Oncol 2015;13:86.
63. Li J, Hou Y, Cai XB, et al. Sorafenib after resection improves the outcome of BCLC stage C hepatocellular carcinoma. World J Gastroenterol 2016;22:4034-40.
64. Guo WX, Guo L, Wang K, et al. Postoperative sorafenib prolongs survival of hepatocellular carcinoma patients with Portal vein tumor thrombus following hepatic resection. Int J Clin Exp Med 2017;10:1615-23.
65. Li N, Feng S, Xue J, et al. Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. HPB (Oxford) 2016;18:549-56.
66. Chen ZH, Zhang XP, Wang K, et al. Liver resection versus transcatheter arterial chemoembolization for the treatment of patients with hepatocellular carcinoma and hepatic vein or inferior vena cava tumor thrombus: A propensity score matching analysis. Hepatol Res 2019;49:441-52.
67. Wei X, Jiang Y, Zhang X, et al. Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular

© HepatoBiliary Surgery and Nutrition. All rights reserved.
https://dx.doi.org/10.21037/hbsn-21-419

Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study. J Clin Oncol 2019;37:2141-51.
68. Matono R, Yoshiya S, Motomura T, et al. Factors linked to longterm survival of patients with hepatocellular carcinoma accompanied by tumour thrombus in the major portal vein after surgical resection. HPB (Oxford) 2012;14:247-53.
69. Kokudo T, Hasegawa K, Matsuyama Y, et al. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: A Japanese nationwide survey. Hepatology 2017;66:510-7.
70. Hatano E, Uemoto S, Yamaue H, et al. Significance of hepatic resection and adjuvant hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombus in the first branch of portal vein and the main portal trunk: a project study for hepatic surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2018;25:395-402.
71. Lee JM, Jang BK, Lee YJ, et al. Survival outcomes of hepatic resection compared with transarterial chemoembolization or sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis. Clin Mol Hepatol 2016;22:160-7.
72. Lee D, Lee HC, An J, et al. Comparison of surgical resection versus transarterial chemoembolization with additional radiation therapy in patients with hepatocellular carcinoma with portal vein invasion. Clin Mol Hepatol 2018;24:144-50.
73. Yu JI, Choi GS, Lim DH, et al. Treatment of Naïve HCC Combined with Segmental or Subsegmental Portal Vein Tumor Thrombosis: Liver Resection Versus TACE Followed by Radiotherapy. Anticancer Res 2018;38:4919-25.
74. Lei HJ, Chau GY, Lui WY, et al. Prognostic value and clinical relevance of the 6th Edition 2002 American Joint Committee on Cancer staging system in patients with resectable hepatocellular carcinoma. J Am Coll Surg 2006;203:426-35.
75. Lei HJ, Chau GY, Lui WY, et al. Prognostic value and clinical relevance of the 6th Edition 2002 American Joint Committee on Cancer staging system in patients with resectable hepatocellular carcinoma. J Am Coll Surg 2006;203:426-35.
76. Chok KS, Cheung TT, Chan SC, et al. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg 2014;38:490-6.
77. 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;10:855-62.
78. Pesi B, Ferrero A, Grazi GL, et al. Liver resection with thrombectomy as a treatment of hepatocellular carcinoma with major vascular invasion: results from a retrospective multicentric study. Am J Surg 2015;210:35-44.
79. Roayaie S, Jibara G, Taouli B, et al. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol 2013;20:3754-60.
80. Lim C, Compagnon P, Sebagh M, et al. Hepatectomy for hepatocellular carcinoma larger than 10 cm: preoperative risk stratification to prevent futile surgery. HPB (Oxford) 2015;17:611-23.
81. Cortese S, Morales J, Martín L, et al. Hepatic resection with thrombectomy in the treatment of hepatocellular carcinoma associated with macrovascular invasion. Cir Esp (Engl Ed) 2020;98:9-17.
82. 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;257:929-37.
83. Ye J, Ye H, Xie S, et al. Indications and treatment of hepatocellular carcinoma with portal vein tumor thrombus based on two classifications. Int J Clin Exp Med 2016;9:9021-32.

© HepatoBiliary Surgery and Nutrition. All rights reserved. https://dx.doi.org/10.21037/hbsn-21-419