

Value of surgical resection compared to transarterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein tumor thrombus: A meta-analysis of hazard ratios from five observational studies

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Backgrounds/Aims: Although systemic therapy is recommended in advanced hepatocellular carcinoma (HCC), treatment options for advanced HCC with portal vein tumor thrombosis (PVTT) are debatable. Recent studies have recommended other treatments, such as surgical resection (SR) and transarterial chemoembolization (TACE). Therefore, we performed a meta-analysis of hazard ratio (HR) for overall survival (OS) between the two modalities using previous reports in order to compare the two treatment options. **Methods:** A systematic review was performed on previously reported data that compared the survival benefits of SR and TACE in patients with advanced HCC with PVTT. Thereafter, the meta-analysis was performed to determine the cumulative HR between the two different treatment groups. We used the HR and 95% CI directly from the original data, when available; however, if these data were unavailable, reconstruction was performed with the secondary data from the original Kaplan-Meier survival curve. **Results:** A total of seven studies were eligible; however, 2 were excluded from the meta-analysis. The remaining 5 studies that included 1422 patients (SR group=559, TACE group=863) were studied for the meta-analysis. The median OS was longer in the SR group (8.2-64 months in SR vs. 6.6-32 months in TACE), proving that SR offered survival benefits. Moreover, the HR for the OS in the TACE group was 1.64 (95% CI, 1.43-1.88) compared to SR group, depicting that TACE was a less favorable option compared to SR. **Conclusions:** There is evidence that SR may be a better viable option for advanced HCC with PVTT. (*Ann Hepatobiliary Pancreat Surg* 2020;24:243-251)

Key Words: Hepatectomy; Hepatic resection; Portal vein invasion; Kaplan-Meier survival data

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed malignancies worldwide. Its incidence has been increasing annually, making it one of the leading causes of cancer-related deaths. Various factors, such as chronic hepatitis B/C infections, advanced age, obesity, alcohol abuse, diabetics, and family history are associated with a higher risk of HCC.¹ The Barcelona Clinic Liver Cancer (BCLC) system is one of the most renowned staging systems for HCC that has provided a guideline for HCC treatment. In the early stages of HCC, interventions with surgical resection (SR), transplantation, and local ablations are recommended and are known to benefit the

patient. In addition, in the stage of HCC, transarterial chemoembolization (TACE) is also helpful. In the advanced stages of HCC, systemic therapy with sorafenib is considered the treatment of choice. However, its effect appears limited because it improves the patients' overall survival (OS) only by few months.²⁻⁴

In advanced HCC, patients either have macrovascular invasion or extrahepatic spread, with poor prognosis. In particular, HCC with portal vein tumor thrombosis (PVTT) is believed to be a negative prognostic factor because it increases the likelihood of tumor cell spread into the bloodstreams, resulting in higher chances of recurrence.⁵ Previous studies have stated that HCC patients with portal vein invasion have a median survival period of 2.7-4 months

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without any treatment.^{6,7} However, as per recent studies, depending on the patient's baseline performance status, hepatic function, tumor characteristics, the type of therapy could increase the survival duration from 5 months to 5 years.^{8,9} Therefore, it is crucial to choose the optimal treatment. As briefly mentioned above, sorafenib was usually recommended. However, with continuous research, other treatments, such as SR and TACE, are available options for treating advanced HCC.^{10,11}

SR is the main treatment option in early HCC and is indicated when there is a solitary tumor in patients without cirrhosis. However, several studies have stated that SR is a possible treatment modality in HCC patients with PVTT, particularly for patients with type I or II PVTT.^{12,13} TACE is the procedure of choice for intermediate stage HCC. Some studies have shown survival benefits in asymptomatic patients with multifocal disease without vascular invasion or extrahepatic spread. It is believed not to be beneficial in portal vein invasion and it is especially contraindicated in PVTT type III and IV because this can lead to necrosis of the hepatic tissue. However, in few studies, TACE appears to be a treatment option in HCC patients with PVTT.^{14,15}

Therefore, it is crucial to evaluate and recognize whether SR or TACE is beneficial in advanced HCC with PVTT and which modality offers more advantages. This will in turn provide other treatment options in addition to sorafenib for patients with advanced HCC with PVTT. Thus, recent studies have compared these treatment modalities in advanced HCC with PVTT. To our knowledge, no randomized-controlled trial has been reported, while some recent meta-analysis studies have focused on this research area. In previous meta-analysis studies, the intervention effect was measured with calculated odds ratios (OR) with the standard error from the original studies.^{16,17} Using this method, time-to-event data was analyzed as dichotomous data. However, the hazard ratio (HR), usually calculated from a Cox proportional hazards model, is the most appropriate way for analyzing survival end points in studies of intervention effect.¹⁸ Thus, we aimed to perform a meta-analysis of HR for overall survival (OS) between two treatment modalities groups. In order to obtain an estimate of the HR, when it is not reported in original studies, the Kaplan-Meier (KM) data were reconstructed from the published survival curves of each study.

MATERIALS AND METHODS

A systematic review of studies reporting on survival, comparing SR to TACE in patients with HCC with PVTT was performed. We exclusively abstracted and then combined in a meta-analysis the HRs from the observational studies. All study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs in both fixed- and random-effects models. This analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Literature search

Electronic searches were performed using MEDLINE, Cochrane Library, and KoreaMed, from their date of inception to December 2019. To obtain the maximum sensitivity of the search strategy and identify all studies, we combined "carcinoma, hepatocellular" as Medical Subject Headings (MeSH) terms or keywords with each of "portal vein" AND "hepatectomy" or "liver resection" or "surgical resection" AND "Transarterial chemoembolization" or "TACE". We also searched reviews about similar issues via manual screening of the reference lists for further identification of potentially relevant studies. Titles and abstracts of retrieved articles were examined to exclude irrelevant reports. For further screening, all the selected articles were systematically assessed using the inclusion and exclusion criteria independently by two investigators (KK and SKS). Disagreements were subjected to discussions for reaching a consensus.

Eligibility criteria

Studies with assessable reports on the survival comparisons in HCC patients with PVTT who underwent SR and TACE were included and were judged suitable for the meta-analysis only if the HR between two treatment modalities or the figures of Kaplan-Meier survival curves were available. When institutions published several similar studies with accumulating data of the involved patients, the most complete reports were used for our final analyses. Studies with sample size <20 for each treatment modality group were excluded. Only publications in English language were considered. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded because of potential publication bias and

result duplication. Primary end points of the study were the assessment of cumulative HR between the two treatment modalities groups.

Survival data extraction and reconstruction of Kaplan–Meier data

Data regarding the author’s first name, publication year, study methods, patient characteristic, interventions, and outcomes were extracted and assessed by two investigators (KK and SKS). We extracted and recorded the HR and 95% CI directly from the original data whenever available. If not, we reconstructed the KM survival data for each treatment group from the published survival curves. The time and survival probability coordinates were extracted from the figures of survival curves using the DigitizeIt software (www.digitizeit.de). We extracted the numbers of patients at risk and the total numbers of events in each treatment group from the text, when available. The KM survival data were reconstructed using a unique algorithm introduced by Guyot et al.¹⁹ that was adopted to inversely solve the KM equations.

Quality assessment

The quality assessment of the included studies was as-

sessed using the modified Newcastle-Ottawa Scale (NOS) that included selection, comparability, and exposure.

Comparison of the survival outcomes according to HR

The reconstructed patient survival data of each treatment group were then aggregated to form combined KM data for estimating the HR and associated variance using a Cox proportional hazards regression model. Endpoints in this meta-analysis were evaluated with HRs and 95% CIs using both fixed- and random-effects model.

Statistical analyses

For survival analysis and HR calculation, “survival” package in R was used. Meta-analyses were performed using “meta” package in R.²⁰ The significance of the pooled HR was evaluated using the Z test ($p < 0.05$ was considered as statistically significant). The heterogeneity across studies was assessed using the I² statistic. The I² statistic was derived from the Q statistic that provides a measure of the proportion of the overall variation attributable to heterogeneity between the studies. Heterogeneity was considered significant if the Q statistic showed $p < 0.05$ and when the I² statistic exceeded 50%.²¹

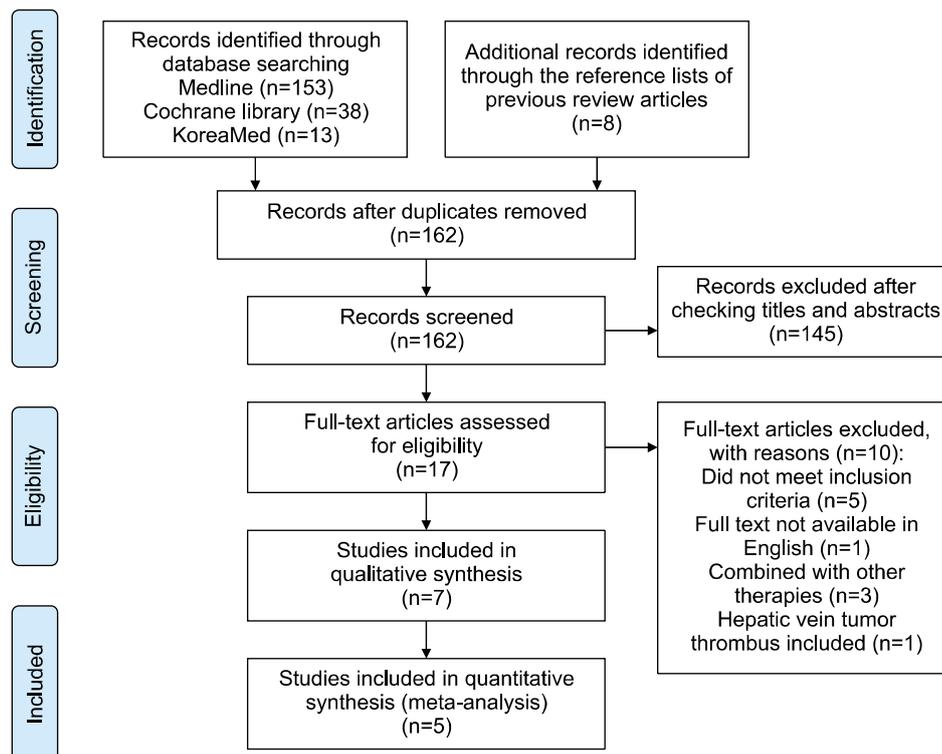


Fig. 1. Flow chart for study selection.

Table 1. Characteristics and baseline demographics of the patients in each included study

Author (year)	Study design (country)	Study period	Group of Tx.	No. of pts. (M/F)	Ages	Type of PVTT (I-II/III-IV)	Tumor (S/M)	Tumor size	CP (A/B)	Etiology (HBV/other)	Cirrhosis (N/Y) or portal HTN (%)
Fan et al. ²² (2005)	Cohort (China)	1997-2002	SR	24 (20/4)	9/15 (<45/≥45)	16/8	14/10	13/11 (<10'/≥10)	18/6/0	NA	NA
Peng et al. ²³ (2012)	Cohort with PS (China)	2002-2007	TACE	53 (40/4)	28/25 (<45/≥45)	30/23	33/20	25/28 (<10'/≥10)	39/14/0	NA	NA
Liu et al. ²⁴ (2014)	Cohort with PS (Taiwan)	2002-2012	SR	201 (187/14)	55 (25-75)	95/105	95/106	76/125 (<5'/≥5)	197/4/0	172/27	25/176
Ye et al. ²⁵ (2014)	Cohort (China)	2007-2009	TACE	402 (374/28)	55 (23-75)	190/212	132/270	178/224 (<5'/≥5)	389/13/0	356/46	39/363
Lee et al. ²⁶ (2016)	Cohort (Korea)	2000-2011	SR	108 (91/17)	62±15	NA	57/51	NA	91/17	50/58	10%*
Zheng et al. ¹² (2016)	Cohort (China)	2000-2008	TACE	108 (84/24)	61±14	NA	56/52	NA	95/13	49/59	33%*
Wang et al. ²⁷ (2016)	Cohort (China)	2002-2014	SR	90 (81/9)	49.3±10.7	66/24	51/39	6.9±1.6	84/6/0	12/78	NA
				86 (80/6)	45.6±10.2	66/20	32/54	6.5±2.7	78/8/0	18/68	NA
				40 (30/10)	55.0±12.9	26/14	NA	20/20 (<5'/≥5)	35/5/0	31 vs 9	13/27 and 5.0%*
				80 (67/13)	58.3±10.5	31/49	NA	10/70 (<5'/≥5)	58/22/0	54/26	7/73 and 33.8%*
				96 (75/21)	51.9±14.3	48/48	NA	7.9±2.2	75/21/0	86 vs 10	17.1%
				134 (98/36)	51.6±13.3	53/71	NA	8.0±2.4	101/33/0	117/17	13.5%
				745 (679/66)	440/305 (<50'/≥50)	614/194	693/52	138/607 (<5'/≥5)	737/8/0	670/75	232/513
				604 (534/70)	285/319 (<50'/≥50)	335/269	474/130	79/525 (<5'/≥5)	567/37/0	125/479	131/473

*percentage of ascites
 CP, Child-Pugh classification; Pts, patients; HTN, hypertension; PVTT, portal vein tumor thrombus; S/M, solitary/multiple; SR, surgical resection; TACE, transarterial chemo-embolization; Tx, treatment

RESULTS

Characteristics of the included studies

In total, 162 non-duplicate records were retrieved. After screening of titles and abstracts, 145 records were excluded and 17 records were assessed for eligibility. The full text of these articles was read, seven retrospective cohort studies^{12,22-27} meeting eligibility criteria were included in the systematic review (Fig. 1). The characteristics and baseline demographic data of the patients in each research study are listed in Table 1. The recruitment period ranged from 1997 to 2012. No prospective studies were found during the search. All studies were from Asia, including one from Korea, one from Taiwan, and five from China. Two studies^{22,27} was excluded from the meta-analysis because the reconstruction of survival data from original KM graph was not possible because no KM survival graph was reported or there were inadequate data of the numbers of patients at risk and the total numbers of events (death). The remaining 5 studies including 1422 patients were finally included in this meta-analysis. The groups were classified as follows: 559 patients in the SR group and 863 patients in the TACE group. Patients enrolled in the systematic review were within Child-Pugh class A or B in all the studies. No study reported statistically significant differences in the baseline demographic or clinical and tumor characteristics of the two groups. The NOS scores of the included studies ranged from 5-7 and were considered of high quality: 5 studies^{12,23-25,27} were scored 6-7 and 2^{22,26} were scored 5.

Comparison of the OS in the SR group and TACE group

In the enrolled studies, the median OS ranged from 8.2-64 months in the SR group and 6.6-32 months in the TACE group. In the SR group, the 1-year OS rate ranged from 22.7%-86.5%, the 3-year OS rate ranged from 0%-69%, and the 5-year OS rate ranged from 0%-69%. In the TACE group, the 1-year OS rate was 11.8%-77.6%, the 3-year OS rate was 0%-50%, and the 5-year OS rate was 0.5%-35%. Based on the original survival data reported in the enrolled studies, the 1-, 3-, and 5-year OS rates were worse for patients receiving TACE than those for patients undergoing SR.

Hazard ratios

To compare the survival outcomes between SR and TACE group, the HR was defined as the ratio of risk of death in the TACE group over the risk of death in the SR group. The HRs of OS could be extracted directly from the original data in three studies,^{23,24,26} however, two studies^{12,25} did not show HR or 95% CI directly in the original paper. To obtain an estimate of the HR from the latter two studies, the Kaplan-Meier data were reconstructed from the published survival curves of each study. Each KM curve of SR and TACE group was extracted separately. Using the algorithm provided by Guyot et al.,¹⁹ the reconstructed KM survival data were obtained that enabled us to reconstruct the KM curves and was used to acquire a reconstructed HR (Fig. 2). With full KM data, the reconstructed HR of one study²⁵ was 1.922 (95%

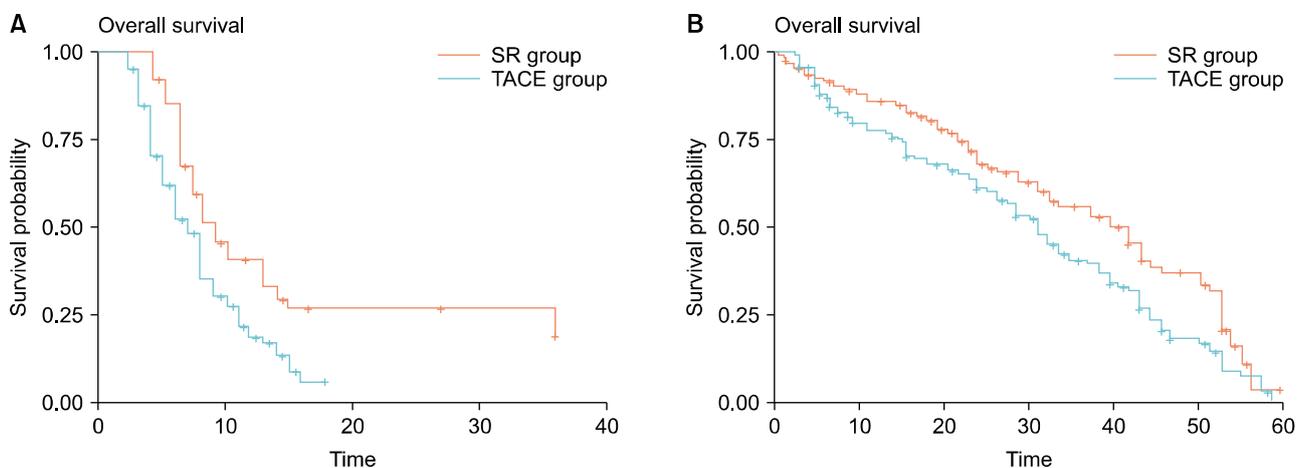


Fig. 2. Reconstructed Kaplan-Meier (KM) survival curves of 2 studies ((A) Ye et al.,²⁵ (B) Zheng et al.¹²) to acquire hazard ratios secondarily from original KM data using the algorithm of Guyot et al.¹⁹

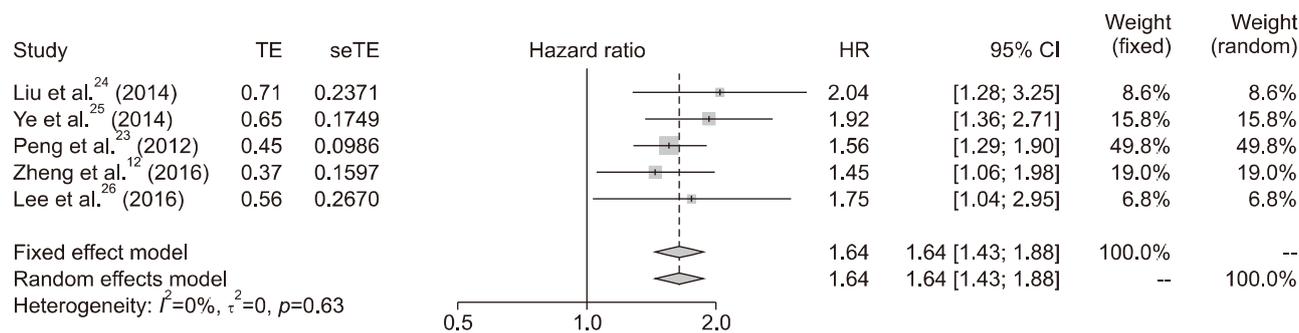


Fig. 3. Forest plot depicting hazard ratio of overall survival in transarterial chemoembolization compared to surgical resection using fixed-effect and random-effect models.

CI, 1.364-2.708) and that of the other study¹² was 1.447 (95% CI, 1.058-1.979).

Endpoints

The OS were compared between the SR group and TACE groups and were evaluated in five of the included studies. Using both the fixed-effect and random-effect models, the pooled HR for the OS in the TACE group was 1.64 (95% CI, 1.43-1.88, Fig. 3) compared to that in the SR group. Heterogeneity was negligible among these studies.

Publication bias analysis

Publication bias analysis was conducted for comparing the primary endpoint between the SR group and the TACE group. There was no apparent publication bias on visual inspection of the funnel plot of the standard error with log HR for overall survival (Fig. 4) or with Egger’s test ($p=0.266$).

DISCUSSION

In clinical oncology, survival analysis is particularly vital because most cancer researches investigate time-to-event endpoints, such as OS and recurrence-free survival. It is also a fundamental aspect of decision-making regarding treatment options and is used to interpret the efficacy of interventions. Survival data are unique in that usually not all patients experience the event by the end of the observation period. For some patients, their actual survival periods are not given. Censoring or incompletely observed survival times are inherent in these data. Survival times of patients may also be skewed; therefore, the use of stat-

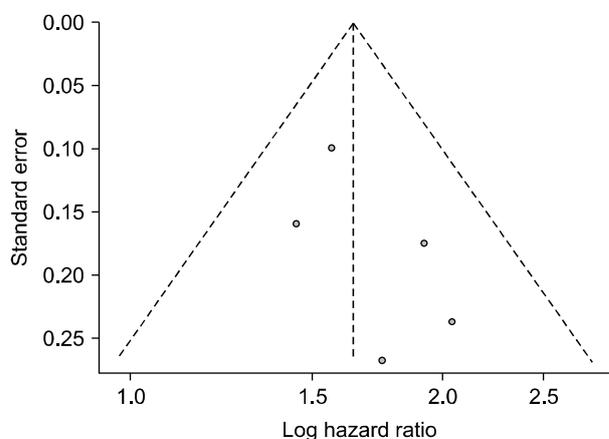


Fig. 4. Funnel plot depicting the publication bias in the included studies.

istical methods that assume a normal data distribution is limited. Therefore, special statistical techniques are needed to compare the survival between the two groups. The risk ratio (relative risk) and OR are relative measures, and are appropriate for measuring dichotomous outcomes. However, they measure only the number of events and neglect the time of occurrence. Thus, they are not appropriate for analyzing time-to-event outcomes. However, HR is usually provided in a Cox proportional hazards model that considers the number and timing of events, and the time until last follow-up for patients without the event. Thus, it is an appropriate method for time-to-event analysis or survival analysis over the entire study duration.^{28,29}

The aim of our meta-analysis was to compare two treatments option (SR and TACE) for HCC patients with PVTT in terms of overall survival. In order to obtain a more robust and reliable estimate of patient survival, we performed a meta-analysis of HRs. Most meta-analyses

combine the data retrieved from different comparative studies with a single endpoint to produce a single pooled result. In this kind of meta-analysis, outcomes are reported as binomial proportions, and the most popular measure of effect is the OR. As mentioned in the previous paragraph, the HR is an appropriate measure in comparing survival analysis, and therefore should be considered a natural quantity when undertaking a meta-analysis of survival studies. Nevertheless, there is a limitation to using HRs in meta-analysis when data regarding HRs are not given. Fortunately, an alternative approach has been proposed when HRs are not available in original articles.¹⁹ Image extraction software (www.digitizeit.de) is used to extract the coordinates of Kaplan-Meier (KM) curves from the original articles. The numbers at risk at follow-up times were calculated using number at risk tables. An algorithm is applied to reconstruct the survival data that are then re-analyzed to report the HR and its respective 95% CI. We utilized this method to obtain HRs from the KM survival curves of two studies (Fig. 2). The calculated HRs were used in the meta-analysis of HRs with original reported HRs from three other studies. This alternative approach appears valuable to reduce the publication bias in meta-analysis when HRs are not reported in the original studies.

In many cases of advanced HCC, there is a simultaneous presence of PVTT. Therefore, in these cases, the surgical procedures may differ, depending on where the tumor thrombosis exists. Tumor thrombectomy can be performed when PVTT does not involve the bifurcation of the portal vein and the tumor thrombus is also contained in the same lobe of the liver as the HCC lesion itself. However, tumor thrombectomy involves the risk of residual tumor. A different surgical technique is recommended when PVTT extends to the portal vein or further, such as en-bloc resection with reconstruction of the portal vein. This technique involves full resection of the vessel containing the tumor thrombus and reconstructing the remaining portal vein in an end-to-end anastomosis manner. This method is complex; therefore, it has higher morbidity and mortality rates but is believed to achieve better oncological outcomes. However, in several studies, tumor thrombectomy had similar survival outcomes with lower operative mortality and morbidity.³⁰⁻³² Therefore, it is difficult to determine which procedure is better than the oth-

er because as per our literature search, there is lack of studies comparing the two different kinds of surgery.

As briefly discussed in the beginning of the article, there are several other treatment options for advanced HCC that have not been included in our study but deserve to be mentioned. Sorafenib, a molecular target agent, has been regarded as the main treatment for advanced HCC. The Sorafenib HCC Assessment Randomized Protocol (SHARP) is a randomized-controlled trial that was conducted in the United States and Europe. In this study, the median overall survival was 10.7 months in the group treated with sorafenib, while that in the control group (placebo group) was 6.9 months. Moreover, the time to progression significantly differed by 5.5 months in the sorafenib group versus 2.9 months in the control group. However, another study on an Asia-Pacific population reported a median OS of 6.5 months for the sorafenib group.^{3,33-36} Another option proposed in recent studies is radioembolization where microspheres containing a specific type of radioactive material are injected into the hepatic artery that becomes entrapped and selectively emits high-dose radiation to the HCC lesion. One study in Italy showed a median OS of 15 months.³⁷ Another trial with fewer advanced HCC patients in Korea showed a 3-year survival rate of 50%-75%.³⁸ However, these treatment options have many diverse adverse effects that may interfere with the patients' consistent compliance to these therapies compared to surgical therapy.

One limitation of our study was that it was based on the secondary data obtained from original papers. Therefore, information on important perioperative variables, such as antiviral drug use and underlying liver disease progression, was not available. These are believed to contribute to tumor recurrence and de novo malignancy. Also, other important considerations in the selection of SR, such as liver function which was only compared by using the Child-Pugh classification in our study, the presence of portal hypertension or low platelet count which reflects the presence of portal hypertension and remnant liver volume which were not available in some of the selected articles could not be accurately assessed in our study. In addition, the present systematic review and meta-analysis included only retrospective studies that are subject to inherent selection bias. The trial also included the geographical limitation of enrolled studies that were all con-

ducted in Eastern Asia and hepatitis B virus-endemic areas. Therefore, further prospective studies on a global level, which include the mentioned limitations above, are necessary.

Our findings showed that SR is a superior treatment option compared to TACE for treating HCC patients with PVTT. Thus, the evidence from these accumulated recent studies that justify the use of SR as a treatment option in advanced HCC patients with PVTT should be used as a stepping stone to assist modifications in the future guidelines for recommended therapies in advanced HCC with PVTT, especially in Eastern Asia. Furthermore, additional intricately designed prospective studies are in need to fully reinforce these findings.

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AUTHOR CONTRIBUTIONS

All authors have contributed significantly: KK, YP. Designed the study: KK, SKS, YP. Analysed and interpreted data: KK, SKS, CWC, YP. Wrote and/or reviewed the manuscript: all authors discussed the results and comment on the manuscript.

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