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### **ABOUT COVER**

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### **AIMS AND SCOPE**

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WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

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META-ANALYSIS

# Transarterial chemoembolization plus stent placement for hepatocellular carcinoma with main portal vein tumor thrombosis: A meta-analysis

### Wei-Fan Sui, Jian-Yun Li, Jian-Hua Fu

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### Abstract

### BACKGROUND

Portal vein tumor thrombus is an important indicator of poor prognosis in patients with hepatocellular carcinoma. Transarterial chemoembolization is recommended as the standard first-line therapy for unresectable hepatocellular carcinoma. Portal vein stent placement is a safe and effective therapy for promptly restoring flow and relieving portal hypertension caused by tumor thrombus.

### AIM

To assess the clinical significance of transarterial chemoembolization plus stent placement for the treatment of hepatocellular carcinoma with main portal vein tumor thrombosis.

### **METHODS**

We searched English and Chinese databases, assessed the quality of the included studies, analyzed the characteristic data, tested heterogeneity, explored heterogeneity, and tested publication bias.

### RESULTS

In total, eight clinical controlled trials were included. The results showed that the pressure in the main portal vein after stent placement was significantly lower than that with no stent placement. The cumulative stent patency and survival rates at 6 and 12 months were lower in the transarterial chemoembolization + stent placement group than in the transarterial chemoembolization + stent placement + brachytherapy/radiotherapy group. The survival rates of patients treated with transarterial chemoembolization + stent placement for 6 and 12 months were higher than those of patients treated with transarterial chemoembolization alone.

### CONCLUSION

For Chinese patients with hepatocellular carcinoma with main portal vein tumor



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thrombosis, transarterial chemoembolization plus stenting is effective. Transarterial chemoembolization + stent placement is more effective than transarterial chemoembolization alone. Transarterial chemoembolization + stent placement + brachytherapy/radiotherapy is more effective than transarterial chemoembolization + stenting.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Portal vein tumor thrombus; Stent; Meta-analysis

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**Core Tip:** Portal vein tumor thrombus (PVTT) as an important indicator of poor prognosis existed in 44% of patients with hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE) is recommended as the standard first-line therapy in unresectable hepatocellular carcinoma. Some Chinese scholars have found that TACE combined with portal vein stent placement is safe and could prolong the survival time in HCC patients with PVTT.

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide[1]. It is the fourth most common malignant tumor and the third most common cause of cancer-related death in China[2]. Portal vein tumor thrombus (PVTT), an important indicator of poor prognosis, occurs in 44% of patients with HCC[3]. PVTT decreases the blood supply to the normal liver and cause deterioration of liver function, gastrointestinal bleeding, and tumor recurrence[4]. HCC with PVTT is regarded as technically unresectable.

Transarterial chemoembolization (TACE) is recommended as the standard first-line therapy for unresectable HCC<sup>[5]</sup>. However, PVTT limits the effect of TACE and leads to liver failure because of portal vein obstruction. Three-dimensional conformal radiotherapy (3-DCRT) and I<sup>125</sup> seeds have been shown to improve survival in HCC patients with main PVTT but not in those with worsened liver function [6,7]. However, the obstruction of the portal vein cannot be relieved immediately by 3-DCRT or I125 seeds alone.

Portal vein stent placement is a safe and effective therapy for promptly restoring flow and relieving portal hypertension caused by tumor thrombus. It prolonged survival in patients with HCC and main PVTT[8]. Several Chinese scholars have shown that TACE combined with portal vein stent placement is safe and can prolong the survival time of HCC patients with main PVTT[9,10]. However, clinical trials with large samples for demonstrating the clinical significance of TACE plus stent placement for HCC patients with main PVTT are currently lacking, and no systematic analysis on the clinical significance of TACE plus stent placement for HCC patients with main PVTT in the Chinese population has been performed. Hence, this study aimed to carry out a meta-analysis to assess the clinical significance of TACE plus stent placement for Chinese patients with HCC and main PVTT.

### MATERIALS AND METHODS

### Search strategy

We performed a comprehensive literature search by using English-language databases, including PubMed, the Cochrane Library, and Excerpt Medica Database, and Chinese databases, including the Chinese National Knowledge Infrastructure (CNKI), Wanfang Data, and CQVIP, up to 2019.

We used the following search terms in the field for title/abstract and/or keywords: "Hepatocellular carcinoma", "transarterial chemoembolization" or "TACE" or "chemoembolization", "portal vein tumor thrombus", and "stent". All the data were available from published papers.

### Study selection

The studies selected met the following inclusion criteria: (1) Original research; (2) human participants; (3) the study had clinical results, such as stent patency rates and survival rates; and (4) the study showed the clinical value of TACE plus stent placement for HCC patients with main PVTT.

### Data extraction and study quality assessment

Two authors screened the titles and abstracts of potentially eligible studies independently and examined the full-text articles to determine whether they could be included. One author independently extracted the data, including author, country, publication year, design, treatment, and patient number. All the included studies were assessed for quality



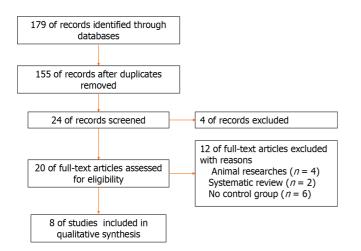


Figure 1 Flowchart of the meta-analysis.

through the Cochrane Collaboration tool[11].

### Data analysis

Review Manager 5.3 was used to analyze the data. For all analyses, P < 0.05 was considered to indicate statistical significance. Heterogeneity was assessed by using the chi-square test and  $l^2$  statistic[12,13]. The  $l^2$  statistic was applied to further assess heterogeneity ( $25\% \le l^2 \le 50\%$  indicated low heterogeneity;  $50\% < l^2 \le 75\%$  indicated moderate heterogeneity). An  $l^2 \ge 75\%$  indicated significant heterogeneity.

Subgroup analysis was performed to explore the source of heterogeneity.

Publication bias was evaluated using funnel plots[13]. When a funnel plot was asymmetrical, interpretation of the results was assessed critically. Otherwise, no publication bias existed.

### RESULTS

### Search strategy

We included eight studies in this meta-analysis. Two studies were published in English[14,15]. Six studies were of Chinese descent[9,10,16-19] (Figure 1).

### Data extraction and study quality assessment

The extracted data included author, publication year, nation, study design, number of patients, and therapies used in the experimental and control groups (Table 1).

The quality of the included studies was assessed. The tool included seven bias metrics, namely, random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. A summary and graphs of the risk of bias were constructed based on the investigators' judgments about each risk of bias item for each included study and are presented as percentages (Figure 2).

### Data analysis

We compared the changes in main portal vein pressure before and after the operation (Figure 3). The pressure in the main portal vein after stent placement was significantly lower than that before stent placement (P < 0.00001), suggesting that stent placement decreased the main portal vein pressure. Heterogeneity existed in these results ( $I^2 = 63\%$ ).

We compared the cumulative stent patency rates at 6 and 12 months (Figure 4). The cumulative stent patency rates at 6 and 12 months were lower in the TACE + stent placement group than in the TACE + stent placement + brachytherapy/radiotherapy group (P < 0.00001), suggesting that stents without brachytherapy/radiotherapy were more obstructed by main PVTT. Heterogeneity did not exist in these results ( $I^2 = 0\%$ ).

We also compared the survival rates at 6 and 12 months (Figure 5). The overall survival (OS) rates at 6 and 12 months were lower in the TACE + stent placement group than in the TACE + stent placement + brachytherapy/radiotherapy group (P < 0.00001), suggesting that TACE + stent placement + brachytherapy/radiotherapy could prolong overall survival better than TACE + stent placement. Heterogeneity existed in these results ( $l^2 = 85\%$ , 27%).

To explore the source of heterogeneity, we performed a subgroup analysis of the overall survival rates at 6 and 12 months (Figure 6). The results showed that the source of heterogeneity was the different therapies: TACE + stent placement + brachytherapy/radiotherapy could prolong overall survival better than TACE + stent therapy, and TACE + stent placement could prolong overall survival better than TACE alone (P < 0.00001).

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### Sui WF et al. Therapy for HCC with main PVTT

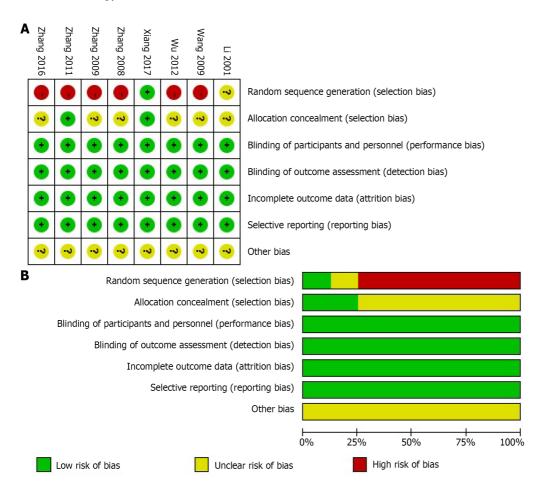


Figure 2 Risk of bias summary and bias graph. A: Review authors' judgements about each risk of bias item for each included study; B: Review authors' judgements about each risk of bias item presented as percentages across all included studies. -: High risk; +: Low risk; ?: Unclear risk.

	Pre-	opera	tion	Post	opera	tion		Std. Mean difference		Std. M	ean diffei	rence	
Study or subgroup	mean	SD	Total	mean	SD	Total	Weight	IV, Random, 95%CI		IV, Ra	ndom, 95	%CI	
Wu 2012	42.1	3.4	50	24.9	2.2	50	42.1%	5.96 [5.03, 6.89]					
Zhang 2016	41.8	5.4	95	15.5	5	95	57.9%	5.03 [4.45, 5.62]			•		
Total (95%Cl)			145			145	100.0%	5.42 [4.53, 6.32]			•		
Heterogeneity: Tau <sup>2</sup> : Test for overall effect					0.10);	<b>I</b> ² = 63	%		-50	-25 pre-opera	0 tion post	25 25	50

### Figure 3 Forest plot of changes of main portal vein pressure.

To assess publication bias, funnel plots were generated, and no publication bias was found (Figure 7).

### DISCUSSION

PVTT is recognized as one of the most significant causes of recurrence and metastasis in HCC patients. The prognosis of HCC patients with PVTT is poor. The portal vein is the main nutrient vessel for the liver. It can be invaded by a tumor thrombus, which causes extensive intrahepatic metastases. When portal vein occlusion is accompanied by tumor thrombus, liver function fails, and the possibility of esophageal gastrointestinal bleeding increases, which is lethal for HCC patients.

Surgical resection can cure PVTT, but the high rate of recurrence after surgery and the high surgical requirements limit its use[20]. 3-DCRT was also used for PVTT. The liver is sensitive to radiation and can tolerate 30 Gy/3-4 wk. However, to cure PVTT, the radiation dose must be above 40 Gy, which can cause external radiation to the liver and body[21]. Because of the tumor thrombus in the hepatic artery, TACE can lead to necrosis of the tumor and tumor thrombus. However, the effect of TACE on tumor thrombi is less than that on tumors because TACE indirectly affects tumor thrombi.

Α	TACE + Stent		TACE + Stent		TACE + Stent		TACE + Stent + 123-I/3-dcrt			Odds ratio	Odds ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%CI	M-H, Fixed, 95%CI					
Li 2011	28	30	26	26	2.1%	0.22 [0.01, 4.69]						
Wang 2009	5	12	8	10	4.6%	0.18 [0.03, 1.23]						
Wu 2012	25	50	40	56	17.1%	0.40 [0.18, 0.89]						
Zhang 2008	6	29	10	16	9.2%	0.16 [0.04, 0.61]						
Zhang 2009	6	29	10	16	9.2%	0.16 [0.04, 0.61]						
Zhang 2016	29	95	140	194	57.8%	0.17 [0.10, 0.29]						
Total (95%Cl)		245		318	100.0%	0.21 [0.14, 0.31]	•					
Total events	99		234									
Heterogeneity: Chi <sup>2</sup> =	3.47, df=	= 5 (P =	0.63); I² = 0%									
Test for overall effect:	Z = 7.88	( <i>P</i> < 0.0)	0001)			0.01	0.1 1 10 TACE + Stent TACE + Stent + 1	100 23-I/3-DCRT				

B TACE + Stent		TACE + Stent + 123-I/3-dcrt			Odds ratio	Odds ratio		
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%CI	M-H, Fixed, 95%CI	
Li 2011	16	30	22	26	11.2%	0.21 [0.06, 0.75]		
Wang 2009	2	12	3	10	2.8%	0.47 [0.06, 3.56]		
Wu 2012	13	50	31	56	22.1%	0.28 [0.12, 0.65]		
Zhang 2008	3	29	5	16	5.9%	0.25 [0.05, 1.25]		
Zhang 2009	3	29	5	16	5.9%	0.25 [0.05, 1.25]		
Zhang 2016	14	95	91	194	52.1%	0.20 [0.10, 0.37]		
Total (95%Cl)		245		318	100.0%	0.23 [0.15, 0.35]	•	
Total events	51		157					
Heterogeneity: Chi <sup>2</sup> =	1.01, df=	5(P = 0	0.96); I² = 0%					
Test for overall effect:	Z = 6.83 (	P ≺0.00	0001)			0.01	0.1 1 10 100 TACE + Stent TACE + Stent + 123-I/3-DCRT	

### Figure 4 Forest plots of cumulative stent patency rates at 6 and 12 months. A: 6 months; B: 12 months.

<b>A</b> Study or subgroup	Experiment: Events	al group Total			Weight	Risk ratio M-H, Fixed, 95%CI	Odds r M-H, Fixed		
Li 2011	13	30	26	26	11.6%	0.01 [0.00, 0.26] 斗			
Wang 2009	5	12	8	10	3.7%	0.18 [0.03, 1.23]	· · · · · ·		
Wu 2012	21	50	37	56	14.7%	0.37 [0.17, 0.82]			
xiang 2017	6	15	4	15	1.7%	1.83 [0.39, 8.57]	9. <u>2</u>	<u> </u>	
Zhang 2008	4	29	13	16	10.5%	0.04 [0.01, 0.19] 🗕			
Zhang 2009	4	29	13	16	10.5%	0.04 [0.01, 0.19] 🔸			
Zhang 2011	18	32	7	30	2.3%	4.22 [1.41, 12.65]			
Zhang 2016	28	95	134	194	45.1%	0.19 [0.11, 0.32]	-		
Total (95%CI)		292		363	100.0%	0.28 [0.20, 0.39]	•		
Total events	99		242						
Heterogeneity: Chi <sup>2</sup> = -	47.84, df = 7 ( <i>P</i>	< 0.0000	01); I <sup>2</sup> = 85%	6				<b>i</b>	
Test for overall effect: 2	Z = 7.48 (P < 0.)	00001)				0.01	. 0.1 1 Experimental group	. 10 Control group	100

<b>B</b> Study or subgroup	Experiment Events		Control Events		Weight	Odds ratio M-H, Fixed, 95%CI		s ratio ed, 95%CI	
Li 2011	0	30	9	26	10.7%	0.03 [0.00, 0.55] 🔸	•		
Wang 2009	2	12	4	10	3.9%	0.30 [0.04, 2.16]			
Wu 2012	7	50	23	56	19.9%	0.23 [0.09, 0.61]			
Zhang 2008	2	29	5	16	6.4%	0.16 [0.03, 0.97]		-	
Zhang 2009	2	29	5	16	6.4%	0.16 [0.03, 0.97]	0	-	
Zhang 2011	3	32	0	30	0.5%	7.24 [0.36, 146.25]			
Zhang 2016	9	95	82	194	52.2%	0.14 [0.07, 0.30]			
Total (95%CI)		277		348	100.0%	0.19 [0.12, 0.31]	•		
Total events	25		128						
Heterogeneity: Chi <sup>2</sup> =	8.19, df = 6 ( <i>P</i>	= 0.22); P	²= 27%			L L		+ +	
Test for overall effect:	Z = 6.91 (P < 0	.00001)				0.0	1 0.1 Experimental group	1 10 Control group	100

### Figure 5 Forest plots of survival rates at 6 and 12 months. A: 6 months; B: 12 months.

According to our meta-analysis, TACE plus a main portal vein stent decreased the pressure in the main portal vein. Furthermore, for HCC patients with main PVTT, TACE plus portal vein stenting improved the survival rate compared with TACE alone. TACE + stent placement + brachytherapy/radiotherapy could improve the stent patency and survival rates better than TACE + stenting. Several studies have shown that portal vein stents serve as palliative remedies for malignant portal vein obstructions and could interrupt the infiltration and ingrowth of tumor thrombi in the portal vein to some degree[8,22], which is consistent with our meta-analysis. However, within a short period, owing to the mesh of the stent, the tumor thrombus might regrow into the stent, leading to reoccurrence and restenosis of the portal vein.

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Α	Experiment	al group	Control	group		Odds ratio	Odds ratio
A Study or subgroup	Events	Total	Events	Total	Weight M	1-H, Fixed, 95%CI	M-H, Fixed, 95%CI
4.1.1 T+S vs T+S+125-	I /3-DCRT						
Li 2011	13	30	26	26	11.6%	0.01 [0.00, 0.26]	+=
Wang 2009	5	12	8	10	3.7%	0.18 [0.03, 1.23]	
Wu 2012	21	50	37	56	14.7%	0.37 [0.17, 0.82]	<b>_</b>
Zhang 2008	4	29	13	16	10.5%	0.04 [0.01, 0.19]	<b>←</b>
Zhang 2009	4	29	13	16	10.5%	0.04 [0.01, 0.19]	<b>←</b>
Zhang 2016	28	95	134	194	45.1%	0.19 [0.11, 0.32]	
Subtotal (95%CI)		245		318	96.0%	0.16 [0.11, 0.24]	•
Total events	75		231				
Heterogeneity: Chi <sup>2</sup> = 1	3.49, df = 5 (P	= 0.02);1	<b>≈</b> =63%				
Test for overall effect: Z	. = 9.28 ( <i>P</i> ≤ 0.	00001)					
4.1.2 T+S vs T							
xiang 2017	6	15	4	15	1.7%	1.83 [0.39, 8.57]	
Zhang 2011	18	32	7	30	2.3%	4.22 [1.41, 12.65]	
Subtotal (95%CI)		47		45	4.0%	3.19 [1.32, 7.74]	-
Total events	24		11				
Heterogeneity: Chi <sup>2</sup> = 0	.75, df = 1 ( <i>P</i> =	= 0.39); l <sup>2</sup> :	= 0%				
Test for overall effect: Z	:= 2.57 ( <i>P</i> = 0.	01)					
Total (95%Cl)		292		363	100.0%	0.28 [0.20, 0.39]	•
Total events	99		242				
Heterogeneity: Chi <sup>2</sup> = 4	7.84. df = 7 (P	< 0.0000	1): I <sup>2</sup> = 85	%			
Test for overall effect: Z						(	0.01 0.1 1 10 100
Test for subaroup diffe	•		= 1 (P < (	0.00001:	. I <sup>2</sup> = 97.3	%	Experimental group Control group

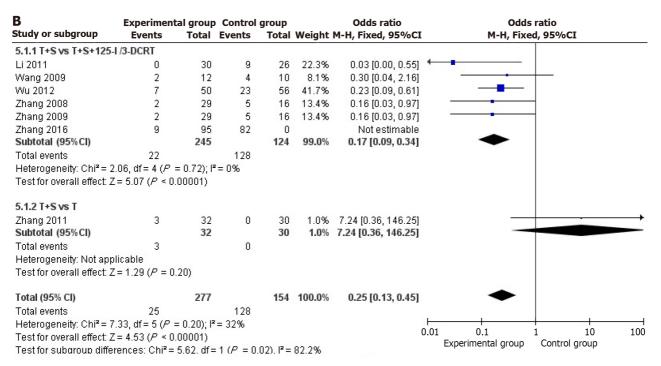


Figure 6 Forest plots of subgroup analysis. A: 6 months; B: 12 months.

Fortunately, TACE + stent placement + brachytherapy/radiotherapy is a practical superior treatment for HCC with main PVTT[14,23]. Because the stent pressed the tumor thrombus, 3-DCRT minimized the likelihood of treating PVTT exactly, which reduced the damage to the normal liver and benefited liver function. I<sup>125</sup> seeds were close to the tumor tissue to deliver continuous irradiation, which restrained the ability of the tumor thrombus to proliferate by damaging the DNA tumor cells. Consequently, the efficiency of TACE + stent placement + brachytherapy/radiotherapy may be better than TACE + stenting and TACE alone for HCC patients with main PVTT. In the future, we can pay more attention to comparing the efficiency of TACE + stent placement + brachytherapy and TACE + stent placement + radiotherapy for HCC patients with main PVTT.

There were several limitations in our meta-analysis: (1) Fifty randomized controlled trials were not included in the selected studies, which may have induced bias and affected our assessment of the management of HCC patients with main PVTT; (2) there was a lack of sufficient statistical data from multiple medical centers available to evaluate the efficacy of different therapies for patients with HCC and main PVTT; and (3) potential publication bias cannot be ignored, although our results showed no significant publication bias.

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Table 1 Characteristics of included studies											
Ref.	Nation	Design	Number of patients (I	M/F)	Therapy						
	Nation	Design	Experimental group	Control group	Experimental group	Control group					
Li et al[ <mark>14</mark> ], 2011	China	NG	23/7	17/9	TACE + stenting	TACE + stenting + I <sup>125</sup>					
Wang <i>et al</i> [16], 2009	China	Retrospective study	12/0	9/1	TACE + stenting	TACE + 3-DCRT					
Wu et al[17], 2012	China	Retrospective study	43/7	51/5	TACE + stenting	TACE + stenting + I <sup>125</sup>					
Xiang <i>et al</i> [9], 2017	China	Prospective study	9/6	8/7	TACE + stenting	TACE					
Zhang <i>et al</i> [18], 2008	China	Retrospective study	28/1	15/1	TACE + stenting	TACE + stenting + 3-DCRT					
Zhang et al[15], 2009	China	Retrospective study	28/1	15/1	TACE + stenting	TACE + stenting + 3-DCRT					
Zhang <i>et al</i> [10], 2011	China	Retrospective study	23/7	22/8	TACE + stenting	TACE					
Zhang et al[19], 2016	China	Retrospective study	83/12	178/16	TACE + stenting	TACE + stenting + I <sup>125</sup>					

NG: Not given.

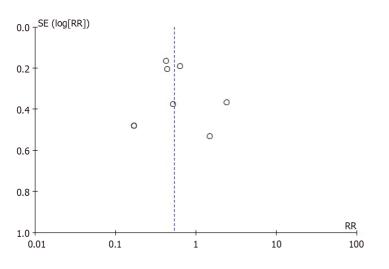


Figure 7 Funnel plot of included studies.

### CONCLUSION

In summary, for HCC patients with main PVTT in the Chinese population, TACE + stent surgery is effective. The therapeutic benefits of TACE + stent placement are better than those of TACE alone. TACE + stent placement + brachytherapy/radiotherapy is more effective than TACE + stent placement.

## **ARTICLE HIGHLIGHTS**

### Research background

Portal vein tumor thrombus (PVTT) has been recognized as an important indicator of poor prognosis for hepatocellular carcinoma (HCC) patients. HCC with main PVTT limits the effect of transarterial chemoembolization (TACE).

### Research motivation

Portal vein stent placement is a safe and effective therapy for promptly restoring flow and relieving portal hypertension caused by tumor thrombus. The efficacy and safety of TACE combined with portal vein stent placement have been proved by some Chinese scholars. No meta-analysis on the clinical significance of TACE plus stent placement for HCC with main PVTT was performed.

### **Research objectives**

This study aimed to carry out a meta-analysis to assess the clinical significance of TACE plus stent placement for HCC with main PVTT.



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### Research methods

We searched English and Chinese databases, assessed the quality of the included studies, analyzed the characteristic data, explored heterogeneity, and tested publication bias.

### **Research results**

The results showed that the pressure in the main portal vein after stent placement was significantly lower than that with no stent placement. The cumulative stent patency and survival rates at 6 and 12 months were lower in the transarterial chemoembolization + stent placement group than in the transarterial chemoembolization + stent placement + brachytherapy/radiotherapy group. The survival rates of patients treated with transarterial chemoembolization + stent placement for 6 and 12 months were greater than those of patients treated with transarterial chemoembolization alone.

### Research conclusions

Transarterial chemoembolization + stenting is safe. Transarterial chemoembolization + stent placement is more effective than transarterial chemoembolization alone. Transarterial chemoembolization + stent placement + brachytherapy/ radiotherapy is more effective than transarterial chemoembolization + stenting.

### Research perspectives

Tyrosine kinase inhibitors and immune therapies have been proved safe and effective. Adding tyrosine kinase inhibitors and immune therapies will improve the value of this study.

### FOOTNOTES

Author contributions: Fu JH designed the research study; Li JY and Sui WF performed the research; Sui WF analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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