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Original Article

The efficacy of surgery and transarterial chemoembolization for hepatocellular carcinoma patients with portal vein tumor thrombus

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Abstract: Background: According to Barcelona Clinic Liver Cancer (BCLC) Group, hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) are defined as BCLC stage C who are recommend with sorafenib. Several studies have found survival benefits followed by hepatectomy and transarterial chemoembolization (TACE) other than recommend therapies. In order to discuss this controversy, we aim to find out which therapy is better for these patients. Methods: From 2010 to 2011, 170 HCC patients were enrolled in this study (surgery group, n=85; TACE group, n=85). Databases were searched to conduct meta-analysis to evaluate the efficacy of surgery and TACE in patients with PVTT. Results: In our study, patients underwent hepatectomy had significantly better survival than patients underwent TACE [mean survival (MS): 17.28 months *vs.* 10.28 months, *P*=0.001]. Patients with PVTT type I (MS: 18.97 months) had significantly longer survival than patients with PVTT type II (MS: 11.71 months, *P*=0.010) and type III (MS: 6.98 months, P<0.001). The difference between patients with PVTT type II or III was also significant (*P*<0.001). Meta-analysis results also showed that patients in surgery group had better 1-year survival [risk ratio (RR)=1.23, 95% confidence interval (CI) 1.09 to 1.39], 2-year survival (RR=1.86, 95% CI 1.54 to 2.24) and 3-year survival (RR=2.09, 95% CI 1.62 to 2.71) than patients in TACE group. Conclusion: The study demonstrated that hepatectomy has potential to improve survival and is safe for HCC patients with PVTT. However, further well-designed controlled trials needs to confirm this effect.

Keywords: Surgery, hepatocellular carcinoma, meta-analysis, portal vein thrombus, transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer worldwide [1]. Approximately 10% to 40% of HCC patients have concurrent portal vein tumor thrombus (PVTT) [2]. PVTT is the independent poor prognostic factors for survival in HCC patients [3, 4].

Surgery still remains the curative therapy, but only available for early stage HCC patients which may provide 5-year survival rate up to 75% [5, 6]. According to Barcelona Clinic Liver Cancer (BCLC) Group, hepatectomy is only suitable for BCLC stage A patients [7, 8]. Patients with PVTT are defined as BCLC stage C for whom sorafenib is recognized as the standard therapy [9, 10]. Although surgery is a not curative therapy for patients with PVTT. However, surgery concludes hepatectomy and thrombectomy were reported to prolong survival [11]. Transarterial chemoembolization (TACE) has been characterized as effective and safe methods for the treatment of HCC patients with PVTT [12, 13]. Also, TACE procedure have been reported to prolong survival periods compared to conservative treatments [14]. Compared with TACE, surgery seems to be more effective and would prolong survival in HCC patients [15]. Nevertheless, rare studies had specifically investigated the survival benefit between surgery and TACE in HCC patients with PVTT.

Therefore, we performed this study to comprehensively compare the safety and efficacy of surgery and TACE for HCC patients with PVTT.

Table 1. Baseline characteristics of HCC patients in each treatment group

	Surgery group (n=85)	TACE group (n=85)	*P* value
Mean age ± SD	50 ± 12	49 ± 16	0.974
Sex (M)	77 (91%)	75 (88%)	0.618
Positive for HBsAg	67 (79%)	68 (80%)	0.850
PLT, 10^9/L	255± 113	267 ± 108	0.814
TBil, μmol/L	19 (11-35)	18 (10-32)	0.926
ALB, g/L	38 ± 7	36 ± 6	0.973
ALT, U/L	42 (22-76)	46 (21-89)	0.249
AST, U/L	45 (27-89)	43 (20-76)	0.841
PT, s	13 ± 1	14 ± 2	0.837
AFP, mg/L	978 (164-1210)	876 (267-1210)	0.230
Child-Pugh A/B	72/13	70/15	0.679
Tumor size, cm	10 ± 5	12 ± 6	0.467
Tumor number (≥3), n	31 (36%)	37 (44%)	0.348
PVTT type, I/II/III	35/25/25	36/27/22	0.868

Notes: TACE: transarterial chemoembolization; PVTT = portal vein tumor thrombus; SD = standard deviation; HBsAg = hepatitis B surface antigen; PLT = platelet count; TBil = total bilirubin; ALB = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = prothrombin time; AFP = alpha-fetoprotein.

Methods

Patients

This retrospective study involved 170 consecutive patients with PVTT admitted to our hospital for treating HCC. According to different therapies, patients were divided into surgery group (n=85), and TACE group (n=85).

Include criteria: (a) 18-75 years old, (b) presence of PVTT type I, II, III (PVTT location not reached the inferior vena cava and mesenteric vein) [16], (c) Child-Pugh liver function stage A or B, (d) patients included in surgery group should have a resectable tumor [15], and (e) diagnosed with HCC based on postoperative pathology. Patients with any previous treatment and patients with other malignant tumors or extra-hepatic metastases were excluded.

Surgical procedure

Patients in surgery group underwent hepatectomy and embolectomy. We recorded the detail data of tumor size, blood loss, operating time, number of tumors, and PVTT location.

During the operation, we used intraoperative ultrasonography to reevaluated PVTT location. Pringle maneuver was used to occlude the blood inflow of the liver distal to the PVTT. After removing the HCC and PVTT, normal saline was used to flush the portal vein and make sure that no PVTT was remained. Then we closed the opened stump.

TACE procedure

We performed Seldinger technique to conduct TACE. Gelatin sponge was used to perform embolization of the tumor feeding artery. After performing embolization, the drug (a mixture of 100 mg cisplatin or oxaliplatin, 30-50 mg doxorubicin), and 5-10 mL of lipiodol were injected.

Follow-up

Patients were asked to reexamine every one month for every 2 months. Reexamination concludes the same test which had done preoperatively. Patients who cannot be found or connected were defined as dead.

Outcomes

We analyzed the OS in 170 HCC patients in order to find out which therapy is better for HCC patients with PVTT. Moreover, we also performed subgroup analysis depending on PVTT type in each therapy group.

Medline database search and meta-analysis

We conducted a meta-analysis to compare the efficacy of surgery and TACE in HCC patients with PVTT in this study to further proved the efficacy of surgery and TACE in patients with PVTT.

MEDLINE, EMBASE, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI) were systematic searched through August 2015 without language restrictions. Eligible studies were identified using any of the following index words: hepatocellular carcinoma *or* HCC *or* liver cancer; transcatheter chemoembolization *or* transarterial chemoembolization *or* TACE; surgery *or* hepatectomy *or* liver resection; portal vein tumor thrombus *or* portal vein tumor thrombi *or* PVTT. Relevant reviews

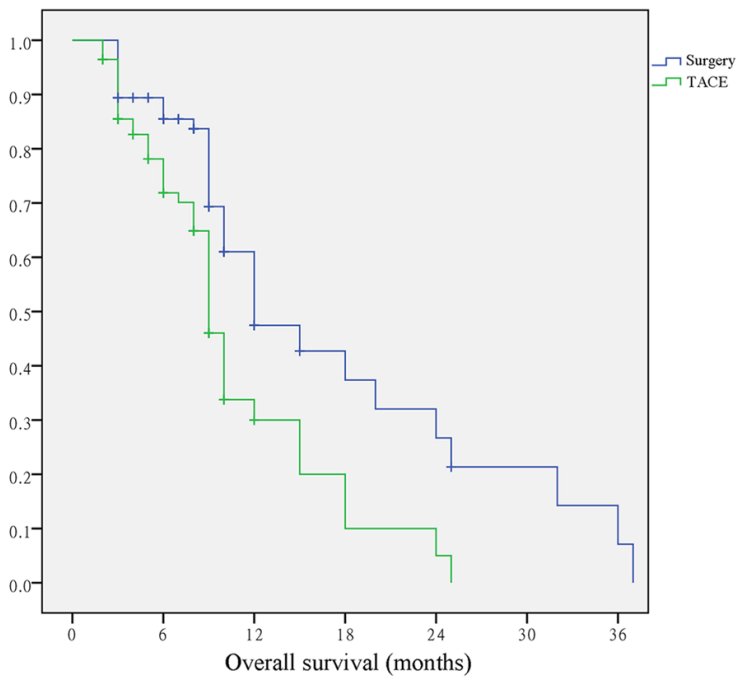

Figure 1. Overall survival between patients in surgery group and TACE group.

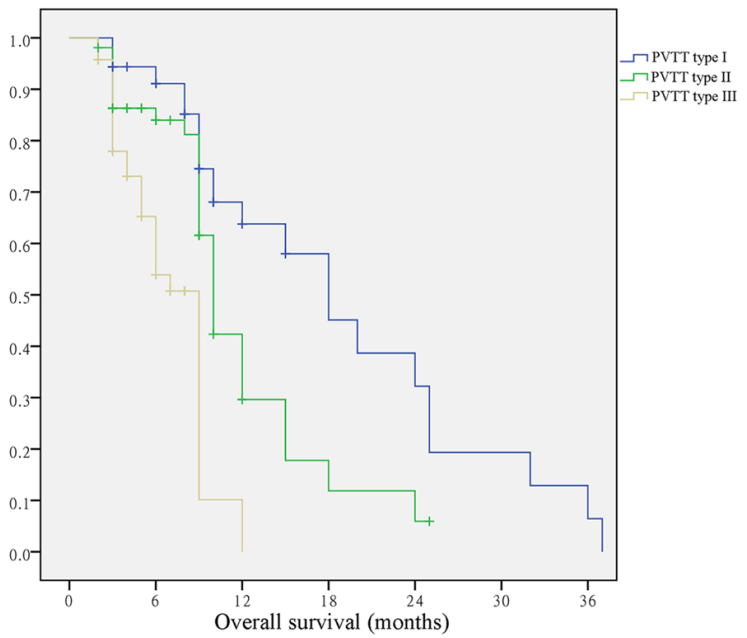

Figure 2. Overall survival in patients with different types of portal vein tumor thrombus.

and meta-analyses comparing Surgery and TACE for HCC patients with PVTT were examined manually to identify additional eligible studies.

Studies would only be included by satisfying following criteria: (1) the trial involving HCC patients with PVTT; (2) the trial conducted the comparison between the treatment of surgery and TACE; (3) the trial reported data on survival outcomes.

Statistical analysis

Original data analyses were performed using SPSS 18.0 (IBM, Chicago, USA). We defined threshold of statistical significance as $P<0.05$. Normally distributed data were expressed as mean ± standard deviation (SD), while asymmetrically distributed data were expressed as median (range). The Kaplan-Meier method was used to calculate OS.

The statistical calculations of meta-analysis used Stata 12.0 (Stata Corp, College Station, TX, USA). Mantel-Haenszel RRs with corresponding 95% CIs were calculated for 1-, 2-, 3-year survival. Heterogeneity was assessed by calculating I^2 (I^2>50%, fixed-effects model; I^2<50%, random-effects model).

Results

Characteristics of the study population

From 2010 to 2011, 170 eligible HCC patients with PVTT were admitted to this retrospective study (surgery group, n=85; TACE group, n=85). Patients' characteristics in both groups were similar (**Table 1**).

Overall survival

Patients underwent surgery (mean survival: 17.28 months) had significantly longer survival time than patients underwent TACE procedure (mean survival: 10.78 months) (P=0.001). The

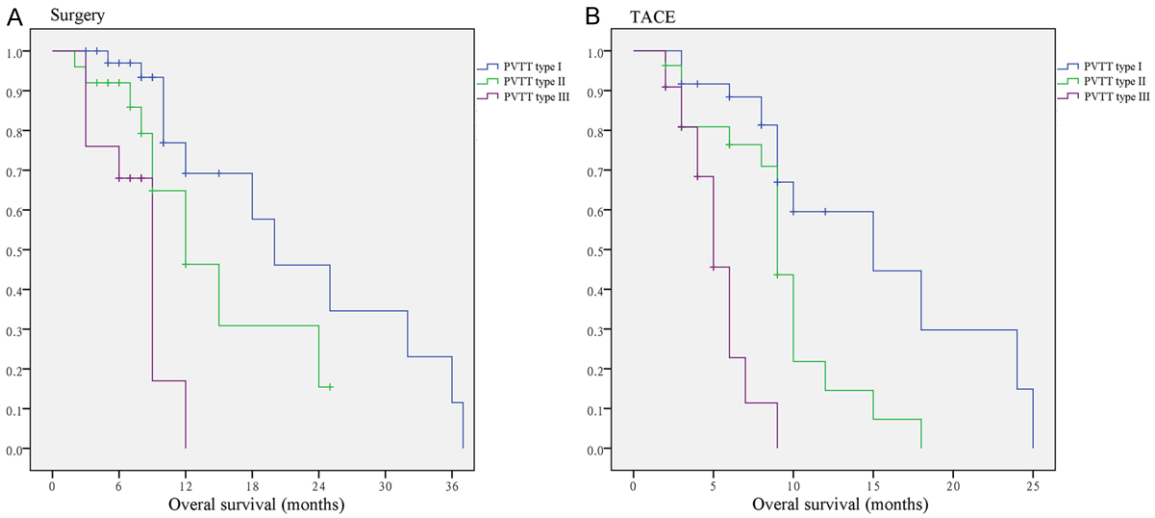

Figure 3. Subgroup analysis in each treatment group depending on different types of portal vein tumor thrombus.

Table 2. Prognostic factors for overall survival

Factor	Patients, n (%)	Univariate Analysis			Multivariate Analysis		
		HR	95% Confidence Interval	P	HR	95% Confidence Interval	P
Treatment							
Surgery	85 (50%)	2.018	1.269-3.210	0.003	2.498	1.554-4.018	<0.001
TACE	85 (50%)						
PVTT type							
e	71 (42%)	2.309	1.671-3.191	<0.001	2.600	1.853-3.648	<0.001
II	52 (30%)						
III	47 (28%)						
Child-Pugh Classification							
A	142 (84%)	1.918	1.012-3.214	0.042	2.276	1.249-5.794	0.134
B	28 (16%)						

Abbreviations: HR, hazard ratio; PVTT, portal vein tumor thrombus.

1-, 2-, 3-year survival rates were 47.5%, 26.7%, 7.1% for patients underwent surgery, and 30.0%, 5.0%, 0.0% for patients underwent TACE procedure (**Figure 1**).

Survival difference among different PVTT types was also analyzed. Patients with PVTT type I (mean survival: 18.97 months) had significantly longer survival than patients with PVTT type II (mean survival: 11.71 months, *P*=0.010) and type III (mean survival: 6.98 months, P<0.001). The difference between patients with PVTT type II or III was also significant (*P*<0.001) (**Figure 2**).

Subgroup analysis

Subgroup analysis depending on PVTT type was conducted in each treatment group. In surgery group, we found patients with PVTT type I (mean survival: 22.23 months) had significantly longer survival than patients with PVTT type III (mean survival: 7.83 months, *P*<0.001) and OS in patients with PVTT type II (mean survival: 14.91 months) was significantly longer than patients with PVTT type III (*P*=0.029). Patients with PVTT type I seemed have a longer OS than PVTT type II patients, but the difference was not significant (*P*=0.069). In TACE group, patients with PVTT type I (mean survival: 15.25

Table 3. Characteristics of included studies comparing hepatectomy and TACE to treat patients with PVTT

Study	Country	Study design	Quality score	Arm	n (male)	Age, yr	Child-Pugh, n (A/B)	HCC etiology, n (HBV/other)	PVTT type, n (I/II/III/IV)
Cheng *et al.* 2005	China	Retrospective	7	Surgery	7 (5)	69.3 ± 11.8	NR	6/1	2/4/1/0
				TACE	38 (35)	68.4 ± 8.5	NR	32/6	6/11/20/1
Fan *et al.* 2005	China	Retrospective	6	Surgery	24 (20)	NR	18/6	NR	16 (I+II)/8 (III+IV)
				TACE	53 (49)	NR	39/14	NR	30 (I+II)/23 (III+IV)
Liu *et al.* 2014	China	Prospective with PSA	9	Surgery	108 (84)	62 ± 15	84/16	48/60	NR
				TACE	108 (78)	61 ± 14	88/12	49/59	NR
Peng *et al.* 2012	China	Retrospective, case-control	8	Surgery	201 (187)	55 (25-75)	197/4	172/29	27/68/83/23
				TACE	402 (374)	55 (23-75)	389/13	356/46	54/136/166/46
Ye *et al.* 2014	China	Retrospective	7	Surgery	90 (81)	49.3 ± 10.7	84/6	12/78	66 (I+II)/24 (III+IV)
				TACE	86 (80)	45.6 ± 10.2	78/8	18/68	66 (I+II)/20 (III+IV)
Our study 2015	China	Retrospective	8	Surgery	85 (77)	50 ± 12	72/13	67/18	35/25/25/0
				TACE	85 (75)	49 ± 16	70/15	68/17	36/27/22/0

Abbreviations: HBV, hepatitis B virus infection; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; NR, not reported; PSA, propensity score analysis; PVTT, portal vein tumor thrombus.

months) had significantly longer survival than patients with PVTT type II (mean survival: 9.16 months, P=0.001) and type III (mean survival: 5.31 months, P<0.001). The difference between patients with PVTT type II or III was also significant (P=0.002) (**Figure 3**).

Prognostic factors for overall survival

We conduct univariate logistic regression analysis and found 3 factors associated with worse OS. Then these 3 factors were enrolled in multiple logistic regression analysis and found patients underwent TACE (hazard ratio (HR) =2.498, 95% CI 1.554 to 4.018, P<0.001), advanced PVTT type (HR=2.600, 95% CI 1.853 to 3.648, P<0.001) were associated with worse OS (**Table 2**).

Medline database research and meta-analysis of included studies

MEDLINE, EMBASE, the Cochrane Library, the Chinese National Knowledge Infrastructure database, and clinical trial registries were searched through Sep. 2015. Totally 214 published studies were initial searched. After manual searching, 201 published trials were removed because they turned out to be systematic reviews, meta-analyses or a conference abstract. Thus, together 5 trials and our study including 1287 patients were enrolled in this analysis. The characteristics of the included studies are shown in **Table 3**.

Five studies [17-21] and this study estimated 1-year survival, and found patients in hepatectomy group had significantly longer 1-year survival rates than patients undergoing TACE procedure (RR=1.23, 95% CI 1.09 to 1.39, I^2=0%). Hepatectomy also had significantly better 2-year survival (RR=1.86, 95% CI 1.54 to 2.24, I^2=81.9%) and 3-year survival (RR=2.09, 95% CI 1.62 to 2.71, I^2=57%) than TACE (**Figure 4**; **Table 4**).

Discussion

Patients with PVTT usually undergo an unsatisfied OS [22]. According to guidelines of EASL, patients with PVTT are only suitable for sorafenib or other palliative therapy [23]. Also, patients with PVTT are often defined as BCLC stage C, and these patients were candidates for sorafenib [24]. However, several studies [25, 26] had figured out patients with PVTT may had survival benefits undergoing hepatectomy or TACE other than sorafenib or other palliative therapy. Since hepatectomy and TACE would bring survival benefit, which treatment is better still remains controversial [4, 27]. Our study aims to find the efficacy and the safety of hepatectomy and TACE in HCC patients with PVTT.

Hepatectomy was once provided for patients with profound liver function, smaller tumor size, and without vessels involvement. In patients with PVTT, they easily occurred portal hypertension and intra-liver metastasis [8]. Advanced tumor stage and symptoms induced by portal hypertension increased the risk and difficulties of hepatectomy. However, the superiority of surgery over other treatments had been demonstrated in many studies [27-29]. Hepatectomy

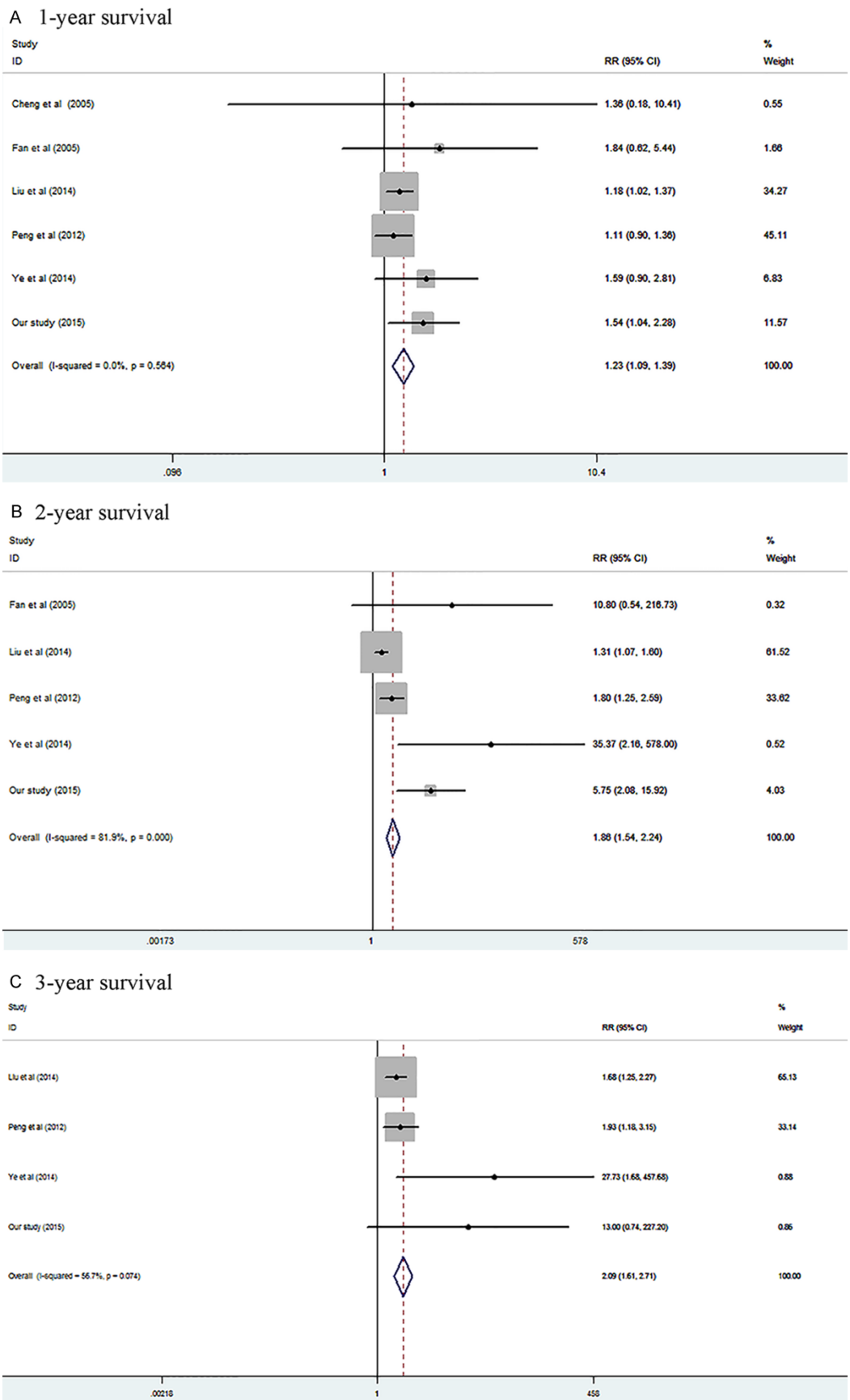

Figure 4. Meta-analysis of data on survival in patients with PVTT following either hepatectomy or TACE.

Table 4. Survival rates and prognostic factors comparing hepatectomy and TACE to treat patients with PVTT

Study	Arm	n	Survival	1 year OS	2 year OS	3 year OS	Prognostic factors for OS
Cheng *et al.* 2005	Surgery	7	8.0 (median)	14.3%	NR	NR	NR
	TACE	38	5.0 (median)	10.5%	NR	NR	
Fan *et al.* 2005	Surgery	24	10.1 (mean)	22.7%	9.8%	0.0%	Strategy of treatment, the number of chemotherapy cycles
	TACE	53	7.3 (mean)	11.8%	0.0%	0.0%	
Liu *et al.* 2014	Surgery	108	64 (median)	84%	74%	59%	AFP level, presence of ascites, strategy of treatment
	TACE	108	32 (median)	71%	56.3%	35%	
Peng *et al.* 2012	Surgery	201	20.0 ± 1.8	42.0%	22.5%	14.1%	Type of PVTT, tumor size, tumor number, initial treatment allocation
	TACE	402	13.1 ± 0.6	37.8%	12.5%	7.3%	
Ye *et al.* 2014	Surgery	90	8.2 (mean)	28.0%	20.0%	15.0%	Strategy of treatment
	TACE	86	7.0 (mean)	17.5%	0.0%	0.0%	
Our study 2015	Surgery	85	17.28 (mean)	47.5%	26.7%	7.1%	Strategy of treatment, PVTT type
	TACE	85	10.78 (mean)	30.0%	5.0%	0.0%	

Abbreviations: AFP, alpha-fetoprotein; TACE, transarterial chemoembolization; NR, not reported; PVTT, portal vein tumor thrombus.

combined with thrombectomy can reduce portal hypertension and thus prevent the occurrence of intractable ascites and bleeding of esophageal varices [18]. Furthermore, the method also allows the recovery of portal vein blood flow, improves liver function, reduces tumor burden. Moreover it could increase the efficacy of postoperative multimodality treatments. Thus to prolong OS [18, 27, 30].

TACE used to be the contradictions for patient with PVTT according to BCLC group [7]. Invisible intrahepatic metastasis via the portal venous system is the primary mechanism for intrahepatic recurrence [31, 32]. Moreover, TACE also increase the incidence of pulmonary metastasis [33]. However, recently a meta-analysis has proved that patients with PVTT could benefit from TACE other than conservative therapy [14].

In our study, we found that patients underwent hepatectomy had significantly longer OS than patients underwent TACE procedure. Also, patients with less advanced PCTT type were associated with a better survival. Subgroup analysis also convinced this finding. Though a similar OS benefit was found between patient with PVTT type I or II after surgery. This may due to the procedure of embolectomy. We should occlude the end of the first branches when PVTT type was I or II. In our meta-analysis, hepatectomy seemed to have better survival outcome than TACE (1-, 2-, 3-year survival). Compared with TACE, hepatectomy reduced the tumor burden and gained patients more chances to receive further therapy thus to prolong the OS. Nevertheless, risk factor analysis of 5 included trials and our study all claimed that surgery remained the prognostic factors for patients with PVTT.

The treatment for HCC patients was multiple. Patients with single use of any treatment seemed to receive unsatisfied OS. Thus, hepatectomy combined with postoperative TACE may provide a good survival outcome. Postoperative TACE can effectively block the tumor's nutrient vessels. In this way a large doses of sustainable chemo drugs could kill the residual microscopic HCC cells without damaging normal liver cells [34, 35].

Our study has several limitations. First, study design was retrospective which would have selection bias. However, baseline characteristics were similar between 2 groups. And further meta-analysis convinced our results. Thus the bias would decreas. Second, PVTT in patients under TACE procedure was evaluated by images. This may have the bias.

In spite of differences in study design and population characteristics, our study demonstrated that hepatectomy has potential to improve survival and is safe for HCC patients with PVTT. However, further well-designed controlled trials needs to confirm this effect.

Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the experiments: H.Z.Y. and J.H.X.. Performed the experiments: H.Z.Y. and W.W.N.. Analyzed the data: H.Z.Y., W.W.N., Y.Q.Z., H.L.H., W.W.H., G.L. and F.Y.C.. Contributed reagents/materials/analysis tools: H.Z.Y. and H.H.Y.. Wrote the paper: H.Z.Y. and J.H.X..

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References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Kuo YH, Lu SN, Chen CL, Cheng YF, Lin CY, Hung CH, Chen CH, Changchien CS, Hsu HC, Hu TH, Lee CM, Wang JH. Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis. Eur J Cancer 2010; 46: 744-751.

[3] Ohkubo T, Yamamoto J, Sugawara Y, Shimada K, Yamasaki S, Makuuchi M, Kosuge T. Surgical results for hepatocellular carcinoma with macroscopic portal vein tumor thrombosis. J Am Coll Surg 2000; 191: 657-660.

[4] Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, Shi M. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol 2001; 18: 413-420.

[5] El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 2008; 134: 1752-1763.

[6] Hsu CY, Hsia CY, Huang YH, Su CW, Lin HC, Lee PC, Loong CC, Chiang JH, Huo TI, Lee SD. Selecting an optimal staging system for hepatocellular carcinoma: comparison of 5 currently used prognostic models. Cancer 2010; 116: 3006-3014.

[7] Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.

[8] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379: 1245-1255.

[9] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.

[10] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.

[11] Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shiina S, Cheng AL, Jia JD, Obi S, Han KH, Jafri W, Chow P, Lim SG, Chawla YK, Budihusodo U, Gani RA, Lesmana CR, Putranto TA, Liaw YF, Sarin SK. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010; 4: 439-474.

[12] European Association For The Study Of The Liver, European Organisation For Research and Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943.

[13] European Association for Study of Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer 2012; 48: 599-641.

[14] Xue TC, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a meta-analysis. BMC Gastroenterol 2013; 13: 60.

[15] Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, Peng T, Xie GS, Li LQ. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 2014; 260: 329-340.

[16] Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC, Cheng SQ. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011; 18: 74-80.

[17] Cheng SQ, Wu MC, Chen H, Shen F, Yang JH, Cong WM, Zhao YX, Wang PJ, Ding GH. [Hepatocellular carcinoma with tumor thrombi in the portal vein. A comparison of therapeutic effects by different treatments]. Zhonghua Zhong Liu Za Zhi 2005; 27: 183-185.

[18] Fan J, Zhou J, Wu ZQ, Qiu SJ, Wang XY, Shi YH, Tang ZY. Efficacy of different treatment strate-

gies for hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 2005; 11: 1215-1219.
[19] Liu PH, Lee YH, Hsia CY, Hsu CY, Huang YH, Chiou YY, Lin HC, Huo TI. Surgical resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. Ann Surg Oncol 2014; 21: 1825-1833.
[20] Peng ZW, Guo RP, Zhang YJ, Lin XJ, Chen MS, Lau WY. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. Cancer 2012; 118: 4725-4736.
[21] Ye JZ, Zhang YQ, Ye HH, Bai T, Ma L, Xiang BD, Li LQ. Appropriate treatment strategies improve survival of hepatocellular carcinoma patients with portal vein tumor thrombus. World J Gastroenterol 2014; 20: 17141-17147.
[22] Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999; 29: 62-67.
[23] de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol 2012; 56 Suppl 1: S75-87.
[24] Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014; 63: 844-855.
[25] Kim KM, Kim JH, Park IS, Ko GY, Yoon HK, Sung KB, Lim YS, Lee HC, Chung YH, Lee YS, Suh DJ. Reappraisal of repeated transarterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein invasion. J Gastroenterol Hepatol 2009; 24: 806-814.
[26] Zhou Q, Wang Y, Zhou X, Peng B, Yang J, Liang L, Li J. Prognostic analysis for treatment modalities in hepatocellular carcinomas with portal vein tumor thrombi. Asian Pac J Cancer Prev 2011; 12: 2847-2850.
[27] Yamada D, Wada H, Kobayashi S, Marubashi S, Eguchi H, Takeda Y, Tanemura M, Umeshita K, Doki Y, Mori M, Nagano H. [A long-term survival case of hepatocellular carcinoma with bone metastasis and inferior vena cava tumor thrombus successfully treated with multidisciplinary therapy]. Gan To Kagaku Ryoho 2010; 37: 2670-2672.
[28] Le Treut YP, Hardwigsen J, Ananian P, Saisse J, Gregoire E, Richa H, Campan P. Resection of hepatocellular carcinoma with tumor thrombus in the major vasculature. A European case-control series. J Gastrointest Surg 2006; 10: 855-862.
[29] Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, Kianmanesh R, Ng IO, Curley SA, Yamaoka Y, Lauwers GY, Vauthey JN. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 2005; 137: 403-410.
[30] Ban D, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y, Kosuge T. Efficacy of a hepatectomy and a tumor thrombectomy for hepatocellular carcinoma with tumor thrombus extending to the main portal vein. J Gastrointest Surg 2009; 13: 1921-1928.
[31] Nagasue N, Ono T, Yamanoi A, Kohno H, El-Assal ON, Taniura H, Uchida M. Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis. Br J Surg 2001; 88: 515-522.
[32] Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003; 197: 753-758.
[33] Wu H, Zhao W, Liu S, Zheng J, Ji G, Xie Y. Pure transcatheter arterial chemoembolization therapy for intrahepatic tumors causes a shrink in pulmonary metastases of hepatocellular carcinoma. Int J Clin Exp Med 2015; 8: 1035-1042.
[34] Ueno K, Miyazono N, Inoue H, Nishida H, Kanetsuki I, Nakajo M. Transcatheter arterial chemoembolization therapy using iodized oil for patients with unresectable hepatocellular carcinoma: evaluation of three kinds of regimens and analysis of prognostic factors. Cancer 2000; 88: 1574-1581.
[35] Huang YH, Wu JC, Lui WY, Chau GY, Tsay SH, Chiang JH, King KL, Huo TI, Chang FY, Lee SD. Prospective case-controlled trial of adjuvant chemotherapy after resection of hepatocellular carcinoma. World J Surg 2000; 24: 551-555.