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ORIGINAL ARTICLE

Retrospective Study

Comprehensive treatments for hepatocellular carcinoma with tumor thrombus in major portal vein

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Abstract

AIM: To evaluate the efficacy of transcatheter arterial chemoembolisation (TACE) compared with surgical intervention and sorafenib for treatment of hepatocellular carcinoma (HCC) in patients with tumor thrombus extending to the main portal vein.

METHODS: From 2009 to 2013, a total of 418 HCC patients with tumor thrombus extending to the main portal vein were enrolled in this study and divided into four groups. These groups underwent different treatments as follows: TACE (n = 307), surgical intervention (n = 54), sorafenib (n = 15) and palliative

treatment (n = 42). Overall survival rates were determined by Kaplan-Meier method, and differences between the groups were identified through log-rank analysis. Cox's proportional hazard model was used to identify the risk factors for survival.

RESULTS: The mean survival periods for patients in the TACE, surgical intervention, sorafenib and palliative treatment groups were 10.39, 4.13, 5.54 and 2.82 mo, respectively. For the TACE group, the 3-, 6-, 12- and 24-mo survival rates were 94.1%, 85.9%, 51.5% and 0.0%, respectively. The corresponding rates were 60.3%, 22.2%, 0.0% and 0.0% for the surgical intervention group and 50.9%, 29.5%, 0.0% and 0.0% for the sorafenib group. Evidently, the results in the TACE group were significantly higher than those in the other groups (P < 0.0001). Furthermore, no significant difference among survival rates was observed between TACE with/without sorafenib (10.22 mo *vs* 10.52 mo, P = 0.615). No significant difference in survival rates was also found among the surgical intervention, sorafenib and palliative treatment groups (P > 0.05). These values significantly increased after TACE with/without sorafenib compared with other treatments (P < 0.05).

CONCLUSION: For HCC patients with tumor thrombus extending to the main portal vein, TACE can yield a higher survival rate than surgical intervention or sorafenib treatment.

Key words: Hepatocellular carcinoma; Portal vein; Tumor thrombus; Sorafenib; Transcatheter arterial chemoembolisation; Surgery

Core tip: This study evaluated the efficacy of transcatheter arterial chemoembolisation (TACE) compared with surgical intervention and sorafenib for treatment of hepatocellular carcinoma (HCC) in patients with tumor thrombus extending to the main portal vein. Results revealed that for HCC patients with tumor thrombus extending to the main portal vein, TACE can yield a higher survival rate than surgical intervention or sorafenib treatment.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide[1] and the third leading cause of cancer-related death[2]. Portal vein tumor thrombus (PVTT) was found invading the main trunk in 10%-15% of patients when they were diagnosed with HCC[3-5]. PVTT is usually correlated with a poor HCC prognosis. The mean survival period for HCC patients with PVTT was only 2.7-4.0 mo compared with 24.4 mo for HCC patients without PVTT[6,7]. Portal vein obstruction by tumor thrombus leads to portal vein hypertension, thereby resulting in heavy deterioration and impairment in liver function, intractable ascites, acute esophageal variceal bleeding and related death, particularly in patients with PVTT invading the main trunk of the portal vein. Furthermore, tumor cells usually spread out through the portal vein system and lead to invisible intrahepatic metastasis[8-11].

According to the guidelines of the European Association for the Study of the Liver[12], American Association for the Study of Liver Disease (AASLD)[13] and Classification Liver Cancer (BCLC) staging system, HCC with PVTT is considered entering an advanced stage, and PVTT is commonly regarded as an absolute or related contraindication for hepatic resection (HR) or transarterial chemoembolisation (TACE). Only sorafenib and palliative treatments are available for HCC treatment[1,11,14]. Interestingly, some reports showed that before the PVTT extended to the main trunk of the portal vein, the HR for HCC patients is feasible to achieve a survival benefit[15-17]. However, when PVTT extended to the main trunk of the portal vein, HR would not provide a survival benefit compared with palliative treatments. Instead, non-surgical treatments, such as TACE or TACE combined with sorafenib[18-20], would be better options. Nevertheless, some studies advocated that eradication of the primary tumor *via* hepatectomy and removal of PVTT through embolectomy[15] would still achieve a survival benefit despite that PVTT has been detected in the main trunk of the portal vein of HCC patients[21,22]. Thus, the proper therapy for HCC patients with PVTT existing in the main trunk of the portal vein remains debatable. The current retrospective study aimed to evaluate the efficacy and safety of different treatments, including TACE, HR, sorafenib and palliative treatments for treating HCC patients with PVTT invading the main trunk of the portal vein.

MATERIALS AND METHODS

This study was approved by the institutional review board of Guangxi Medical University and conducted in accordance with the Declaration of Helsinki and current ethical guidelines.

Patients

From January 2009 to December 2013, a total of 418 patients at the Hepatobiliary Surgery Department and Interventional Therapy Department of Guangxi Tumor Hospital, who were diagnosed with HCC combined with PVTT invading the main trunk of the portal vein and had satisfied the inclusion criteria below, were

recruited and retrospectively studied.

The inclusion criteria were: (1) All the candidates recruited were diagnosed with HCC associated with tumor thrombus involving the main trunk of the portal vein, which was defined by the presence of thrombus adjacent to the tumor and in the main trunk of the portal hepatic vein with undefined boundaries, as confirmed by two imaging modalities, namely, computed tomography (CT) and magnetic resonance imaging (MRI)[23], without distant metastasis and were evaluated with the Eastern Cooperative Oncology Group performance status (ECOG)[24] scores of 0-2 and moderate liver function (Child-Pugh A or B); (2) For candidates who underwent surgery, solitary tumor and/or multiple nodules can be eradicated *via* hepatectomy, and PVTT can be removed through embolectomy[15]; the remnant liver volume and liver function reserve were determined by volumetric computed tomography[25,26]. For patients without cirrhosis, approximately 30% of residual liver volume after surgery was considered sufficient, whereas for patients with chronic HBV and liver cirrhosis, the remnant liver volume should be > 50%. HCC and PVTT diagnoses were confirmed by histological examination of surgical samples; (3) For candidates receiving TACE, the inclusion criteria were similar to those in the HR group; these criteria were used when deciding whether to utilise TACE. Moreover, TACE was given to those patients with insufficient remnant liver volume and liver function reserve if they would undergo hepatic resection, with other unfavourable factors for surgery or without strong aspiration to receive HR. Moreover, sorafenib was given as an adjuvant therapy after TACE if possible; (4) For patients with unfavourable factors for HR or TACE, sorafenib was given; and (5) Routine palliative therapy was performed in patients who were not suitable for HR or TACE and did not use sorafenib.

TACE procedure

Contrast medium was injected into the arteries *via* a 4.1-French RC1 catheter, which was introduced into the abdominal aorta *via* the right superficial femoral artery by using the Seldinger technique[27]. Afterwards, the number, location, size and arterial branches supplying the tumors were identified. Iodised oil (10-20 mL), gel foam particles with doxorubicin (30-50 mg) and cisplatinum (50-100 mg) were injected into the arterial branches. Serum total bilirubin, albumin and prothrombin time were routinely monitored on the first, second and third day after TACE. After 1 month, CT follow-up was conducted to determine the effects of TACE. On the basis of liver function and tumor shrinkage, TACE was repeated at one-month intervals, and the TACE cycles were dependent on the tumor response to TACE and patient's liver function.

HR

Left, right, left partial, right partial and partial median hemihepatectomies were performed in 11, 10, 11, 11 and 11 patients, respectively. PVTT was removed in all patients through embolectomy[15]. The operative procedure for PVTT was decided on the basis of the location and extent of tumor thrombus: (1) when tumor thrombus involved the main trunk of the portal vein but not involved the branches of healthy side, surgery was performed to block the portal vein branch of the healthy side and longitudinally incised along the main trunk of the portal vein, the tumor thrombus was removed, and finally, the wall of the portal vein was closed *via* a continuous suture; and (2) when tumor thrombus had grown into the main trunk of the portal vein and branches of the healthy side, surgery was performed to block the portal vein branch of the retention sides to reduce bleeding and longitudinally cut open along the main trunk of the portal vein; the tumor thrombus was removed, and the wall of the portal vein was finally closed *via* a continuous suture. Ultrasound was generally used to detect whether tumor thrombus was completely removed.

Sorafenib administration (sorafenib monotherapy or sorafenib plus TACE)

Generally, about 400 mg of sorafenib (Bayer HealthCare AG, 200 mg/pill) was orally given twice daily. When grade 3 or 4 adverse events (such as skin, hematologic and gastrointestinal toxicities or organ dysfunction defined by the National Cancer Institute Common Terminology Criteria for Adverse Events[28]) occurred, the oral dose was reduced to 200 mg per day. If these adverse events continued after dose adjustment, sorafenib treatment was stopped until the symptoms were reduced or eliminated.

Follow-up and treatment of recurrence

After the initial therapy, serum alpha-fetoprotein (AFP) level and other laboratory tests were routinely monitored; ultrasonography, dynamic CT, MRI or angiography was performed at the end of the first month and then every 3 mo. When intrahepatic recurrence was suspended but not confirmed by imaging or serum AFP level, TACE was applied. When intrahepatic recurrence was confirmed after the initial HR, the second HR was performed on the basis of volumetric CT[25,26]. If HR was not feasible because of poor liver function, numerous intrahepatic metastases or other unfavourable factors, microwave coagulation, percutaneous ethanol injection, radiofrequency ablation or sorafenib therapy were applied instead of TACE. All patients were followed until December 30, 2013 or until death.

Statistical analysis

All the data were analysed using SPSS 21.0 statistical software. Normally and asymmetrically distributed data were determined as mean ± standard deviation (SD) and median (range) values, respectively. The

Table 1 Characteristics of hepatocellular carcinoma patient with portal vein tumor thrombus invading the main portal vein trunk and inferior vena cava *n* (%)

	Group 1 (*n* = 307)			Group 2 (*n* = 54)	Group 3 (*n* = 15)	Group 4 (*n* = 42)	*P* value
	TACE (*n* = 274)	TACE-sorafenib (*n* = 33)	*P* value				
Baseline characteristic							
Age, mean ± SD	48.62 ± 12.09	49.51 ± 11.23	0.764	47.40 ± 17.48	49.78 ± 21.26	51.49 ± 23.23	0.668
Sex (M)	233 (85.0)	26 (78.8)	0.350	46 (85.2)	12 (80.0)	36 (85.7)	0.960
Clinical characteristic							
Positive for HBsAg	224 (81.8)	29 (87.9)	0.505	46 (85.2)	14 (93.3)	36 (85.7)	0.665
Positive for anti-HCV	16 (5.8)	0 (0.0)	0.234	1 (1.9)	0 (0.0)	1 (2.3)	0.755
PLT (10^9/L)	198.25 ± 88.17	205.94 ± 102.04	0.146	246.37 ± 71.13	211.74 ± 101.21	297.10 ± 148.07	0.654
TBil (μmol/L)	19.1 (13.08-30.10)	16.70 (11.80-23.00)	0.347	21.1 (11.46-32.37)	17.23 (10.79-35.69)	25.1 (10.78-41.76)	0.065
ALB (g/L)	37.29 ± 5.14	37.74 ± 4.64	0.981	39.31 ± 7.81	36.73 ± 4.27	32.13 ± 8.23	0.851
ALT (U/L)	54.00 (35.00-79.00)	52.00 (35.00-99.00)	0.813	52.00 (32.00-77.00)	56.00 (31.00-72.00)	58.00 (31.00-81.00)	0.135
AST (U/L)	79.00 (49.00-144.00)	80.00 (50.00-157.50)	0.843	65.00 (28.00-101.00)	78.00 (45.00-127.00)	75.00 (21.00-167.00)	0.104
PT (s)	13.75 ± 1.52	13.84 ± 1.934	0.963	12.11 ± 1.41	13.49 ± 1.37	13.79 ± 1.54	0.060
AFP (mg/L)	873 (126-12100)	1210 (123-12100)	0.107	745 (310-12100)	691 (348-12100)	1207 (1001-12100)	0.793
Child-Pugh Score	5 (5-8)	5 (5-8)	0.914	5 (5-8)	6 (5-8)	6 (5-9)	0.255
Ascites	8 (2.9)	0 (0.0)	0.999	0 (0.0)	0 (0.0)	3 (7.1)	0.201
Pathological characteristic							
Tumor size (cm)	6.78 ± 2.96	7.14 ± 3.97	0.101	7.13 ± 2.73	6.97 ± 2.37	7.95 ± 3.34	0.437
Tumor number (≥ 3), *n*	178 (65.0)	22 (66.7)	0.846	17 (32.4)	9 (60.0)	27 (64.2)	0.982
Cirrhosis, *n*	223 (81.0)	27 (81.8)	0.952	46 (85.2)	11 (73.3)	36 (88.1)	0.697
Portal vein hypertension, *n*	76 (27.7)	8 (24.2)	0.671	12 (22.2)	3 (20.0)	14 (33.3)	0.609
Main portal vein trunk, *n*	211 (77.0)	21 (63.6)	0.091	44 (81.5)	6 (77.0)	17 (77.0)	< 0.001
Inferior vena cava, *n*	63 (23.0)	12 (36.4)		10 (18.5)	9 (77.0)	25 (77.0)	

PVTT: Portal vein tumor thrombus; SD: Standard deviation; HBsAg: Hepatitis B surface antigen; anti-HCV: Hepatitis C virus antibody; PLT: Platelet count; TBil: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; AFP: Alpha-fetoprotein; Group 1: TACE; Group 2: Surgery + postoperative TACE; Group 3: Monotherapy of sorafenib; Group 4: Palliative therapy.

Table 2 Survival period and survival rate in different groups

	Mean overall survival (mo)	3-mo survival rate	6-mo survival rate	12-mo survival rate	24-mo survival rate
TACE administration	10.39	94.1%	85.9%	51.5%	0.0%
TACE subgroup	10.22	93.8%	86.7%	43.9%	0.0%
TACE-sorafenib subgroup	10.52	95.3%	83.3%	53.8%	0.0%
Liver resection + TACE	4.13	60.3%	22.2%	0.0%	0.0%
Targeted therapy of sorafenib	3.54	50.9%	29.5%	0.0%	0.0%
Palliate treatment	2.82	55.0%	0.0%	0.0%	0.0%

TACE: Transcatheter arterial chemoembolization.

baseline characteristics for patients with PVTT invading the main trunk and IVC were calculated using χ^2 tests. Survival time was defined as the period between the initial treatment and date of death or end of the study for survival patients. Survival curves were determined by Kaplan-Meier method, and differences between groups were identified using log-rank analysis. A *P* value < 0.05 was considered statistically significant.

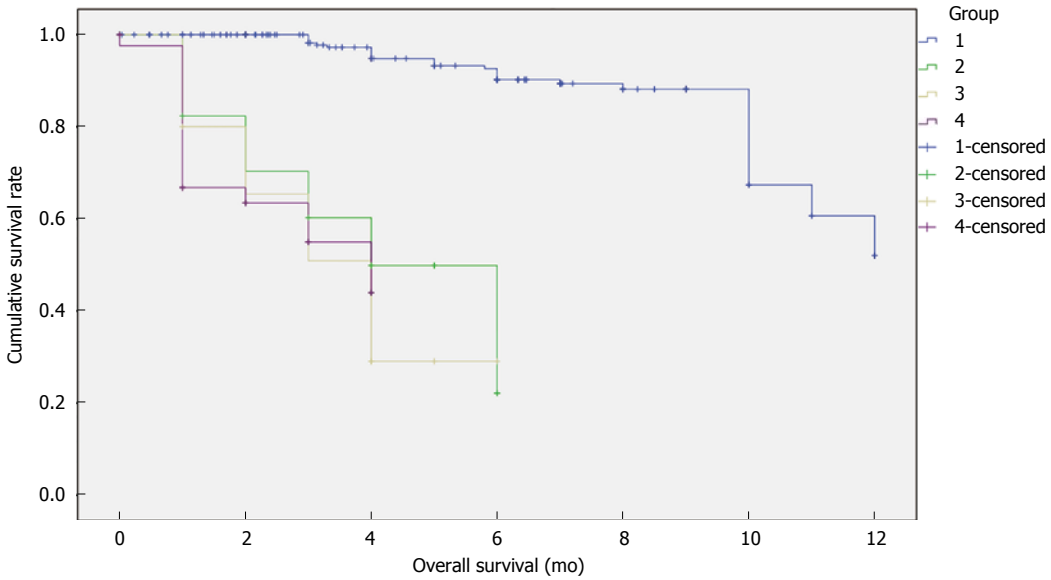
RESULTS

Characteristics of patients

Table 1 summarises the clinical characteristics of the 418 HCC patients. Patients who used sorafenib or underwent palliative treatment were characterised with significantly higher levels of total bilirubin, higher frequencies of PHT and larger and multinodular HCC tumors ($P < 0.001$ for all). No statistical differences were found regarding the clinical or pathological variables, including sex, age, serum AFP level, hepatitis B surface antigen, Child-Pugh classification, ECOG score and location of PVTT among the four groups ($P > 0.05$).

Overall survival periods

The overall survival (OS) periods significantly increased in the TACE group compared with the other groups. For TACE administration, the OS rates at 3, 6, 12 and 24 mo were 94.1%, 85.9%, 51.5% and 0.0%, respectively. The mean survival period was 10.39 mo, which was significantly longer than that obtained from the three other groups ($P < 0.05$) (Figure 1, Table 2). We conducted subgroup analysis to explore



Group[1]	1	2	3	4
mean ± SD (mo)	10.39 ± 5.24	4.13 ± 1.78	3.54 ± 1.38	2.82 ± 1.40
1 (*P* value)	-	< 0.001	< 0.001	< 0.001
2 (*P* value)	< 0.001	-	0.356	0.398
3 (*P* value)	< 0.001	0.356	-	0.781
4 (*P* value)	< 0.001	0.398	0.781	-

Figure 1 Overall survival periods significantly increase in the transcatheter arterial chemoembolisation group compared with the other groups. [1]Group 1: TACE administration; Group 2: Surgery + postoperative TACE; Group 3: Monotherapy of sorafenib; Group 4: Palliative therapy.

the efficacy and safety of sorafenib as an adjuvant treatment for TACE. The 3-, 6-, 12- and 24-mo OS rates were 93.4%, 86.7%, 43.9% and 0.0% for TACE; correspondingly, these rates were 95.3%, 83.3%, 53.8% and 0.0% for TACE together with sorafenib. The mean survival periods were 10.22 and 10.52 mo for TACE alone and TACE together with sorafenib, respectively, which showed no significant difference (Figure 2, Table 2).

In the HR group, the 3-, 6-, 12- and 24-mo OS rates were 60.3%, 22.2%, 0.0% and 0.0%, respectively; correspondingly, these rates were 50.9%, 29.5%, 0.0% and 0.0%, and 55.0%, 0.0%, 0.0%, 0.0% in the sorafenib and palliative treatment groups, respectively. The mean survival periods were 4.13, 3.54 and 2.82 mo in the HR, sorafenib and palliative groups, respectively, in which the palliative group had the lowest mean survival period. Nevertheless, the difference of the mean survival period was not significant among these three groups ($P > 0.05$) (Figure 1, Table 2).

Compilations

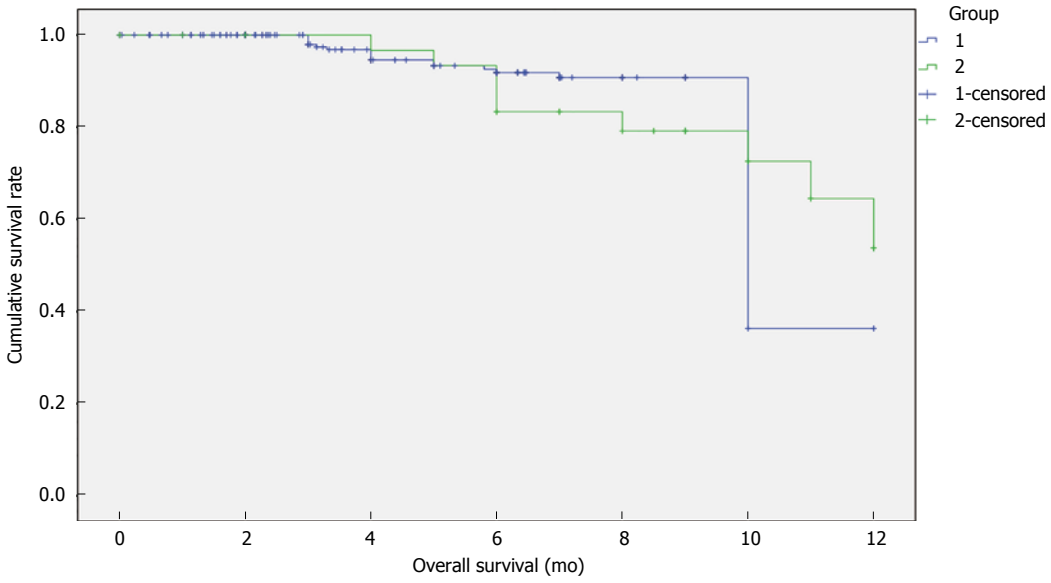
In the HR group, 4 (7.4%) and 2 (3.7%) patients presented postoperative bile leakage and bleeding of esophageal venous plexus, respectively; in addition, 5 (9.3%) patients suffered from postoperative liver function deficiency, of whom 3 (5.6%) had developed refractory ascites and finally died of liver failure. A total of 7 (13.0%) patients suffered from pulmonary complication, and one of them was a 75-year-old man who developed liver abscess and finally died because of serious infection. The PVTT of three patients was observed invading the main portal vein trunk preoperatively but found extending to the IVC during the operation for tumor thrombus; another PVTT was found in the right atrium. Although the tumor thrombus was successfully removed, the patient still died on the 31st day after surgery because of heart failure (1.5%). Table 3 shows a list of other complications. The frequency of complications (44.7%) and death in the hospital (9.3%) after HR were the highest.

Patients who underwent TACE usually had post-embolisation syndrome (nausea, vomiting, fever and pain). One patient also suffered from ectopic embolisation syndrome, and another suffered pulmonary complications and infection. However, no one suffered serious adverse events and hospital death (Table 3).

Most of the patients who used sorafenib suffered from grade 1 or 2 adverse events, and only six patients suffered grade 3 or 4 adverse events (Table 4). Nevertheless, adverse events disappeared after an oral dose reduction.

Analysis of prognostic factors for OS

Multivariate analysis of prognostic factors for OS showed that tumor size [hazard ratios (HR) = 3.31, 95%CI: 1.20-3.30, $P = 0.008$], tumor number (HR = 2.10, 95%CI: 1.22-3.63, $P = 0.007$), serum AFP level (HR = 1.84, 95%CI: 1.09-3.11, $P = 0.023$), Child-Pugh stage (HR = 1.99, 95%CI: 1.20-3.30, $P = 0.008$),



	TACE subgroup	TACE ± sorafenib subgroup	*P* value
Overall survival (mo ± SD)	10.22 ± 4.74	10.52 ± 4.27	0.615

Figure 2 Overall survival between subgroups of transarterial chemoembolisation administrations among all the hepatocellular carcinoma patients with portal vein tumor thrombus extending to the main portal vein trunk and inferior vena cava. TACE: Transarterial chemoembolization; HCC: Hepatocellular carcinoma.

Table 3 Complications and adverse events in different therapy groups *n* (%)

Complication	Group 1 (*n* = 307)			Group 2 (*n* = 54)	Group 3 (*n* = 15)	*P* value
	TACE (*n* = 274)	TACE-sorafenib (*n* = 33)	*P* value			
Nausea, vomiting	49 (17.9)	19 (57.6)	< 0.001	12 (22.2)	12 (80.0)	< 0.001
Fever	62 (22.6)	8 (24.2)	0.835	11 (20.4)	0 (0.0)	< 0.001
Pain	119 (43.4)	7 (21.2)	0.047	24 (44.4)	0 (0.0)	< 0.001
Alopecia	3 (1.1)	11 (33.3)	< 0.001	3 (5.6)	6 (40.0)	< 0.001
Bleeding of tumor rupture	0 (0.0)	2 (6.0)	< 0.001	0 (0.0)	0 (0.0)	< 0.001
Liver failure	1 (0.4)	25 (75.8)	< 0.001	5 (9.3)	4 (26.7)	< 0.001
Bile leakage	0 (0.0)	0 (0.0)	0.999	4 (7.4)	0 (0.0)	< 0.001
Bleeding of esophageal venous plexus	0 (0.0)	0 (0.0)	0.999	2 (3.7)	0 (0.0)	< 0.001
Gastrointestinal hemorrhage	0 (0.0)	1 (3.0)	0.004	1 (1.9)	1 (6.7)	< 0.001
Heart failure	0 (0.0)	0 (0.0)	0.999	1 (1.9)	0 (0.0)	< 0.001
Infection	1 (0.4)	0 (0.0)	0.999	1 (1.9)	0 (0.0)	< 0.001
Ectopic embolism syndrome	1 (0.4)	0 (0.0)	0.999	0 (0.0)	0 (0.0)	< 0.001
Refractory ascites	0 (0.0)	0 (0.0)	0.999	3 (5.6)	0 (0.0)	< 0.001
Pulmonary complication	1 (0.4)	1 (3.0)	0.072	7 (13.0)	0 (0.0)	< 0.001
Therapy-related death	0 (0.0)	0 (0.0)	0.999	5[1] (9.3)	0 (0.0)	< 0.001

[1]Three patients died of postoperative liver failure, 1 patient was observed in right atrium and died of heart failure, and 1 patient died of badly infection. Group 1: TACE; Group 2: Surgery + postoperative TACE; Group 3: Monotherapy of sorafenib; Group 4: Palliative therapy.

cirrhosis (HR= 2.10, 95%CI: 1.02-4.32, *P* = 0.044), PHT (HR = 1.65, 95%CI: 1.02-2.65, *P* = 0.041), and PVTT location (HR = 5.41, 95%CI: 2.66-7.65, *P* < 0.001) were associated with worse OS (Table 5).

DISCUSSION

According to the guidelines of the European Association for Study of the Liver[12], AASLD[13] and Classification Liver Cancer (BCLC) staging system, PVTT was usually considered an absolute or relative contradiction for hepatic resection or TACE, and only sorafenib and palliative treatments are recommended[1,11,14]. However, some studies[15-17] advocated that liver resection and removing tumor thrombus from the portal vein system[21,22], TACE[18-20] and TACE combined with sorafenib[29] still achieved survival benefit despite that the tumor thrombus had extended to the main trunk of the portal vein in HCC patients. Thus, the present study aimed to evaluate the efficacy and safety of different treatments for HCC patients with PVTT involving the main trunk of the portal vein.

TACE remains a safe and effective treatment strategy for HCC

TACE is usually considered a contradiction for HCC

Table 4 Adverse events related to sorafenib administration *n* (%)

Adverse event	Mono-therapy of sorafenib			TACE combined with sorafenib		
	All events	Grade 1-2 events	Grade 3-4 events	All events	Grade 1-2 events	Grade 3-4 events
Overall incidence	14 (93.3)	12 (80.0)	2 (13.3)	30 (90.9)	26 (78.8)	4 (12.1)
Alopecia	6 (40.0)	6 (40.0)	0 (0.0)	11 (33.3)	11 (33.3)	0 (0.0)
Anorexia	4 (26.7)	4 (26.7)	0 (0.0)	18 (54.5)	18 (54.5)	0 (0.0)
Diarrhea	13 (86.7)	12 (80.0)	1 (6.7)	27 (81.8)	26 (78.8)	1 (3.0)
Epistaxis	1 (6.7)	1 (6.7)	0 (0.0)	2 (6.0)	2 (6.0)	0 (0.0)
Fatigue	12 (80.0)	12 (80.0)	0 (0.0)	22 (66.7)	21 (63.6)	1 (3.0)
Gastrointestinal hemorrhage	1 (6.7)	1 (6.7)	0 (0.0)	1 (3.0)	1 (3.0)	0 (0.0)
Hand-foot skin reactions	11 (73.3)	10 (66.7)	0 (0.0)	12 (36.3)	11 (33.3)	1 (3.0)
Liver dysfunction	4 (26.7)	4 (26.7)	1 (6.7)	25 (75.8)	23 (69.7)	2 (6.0)
Nausea	12 (80.0)	12 (80.0)	0 (0.0)	19 (57.6)	19 (57.6)	0 (0.0)

TACE: Transcatheter arterial chemoembolization.

patients with portal vein obstruction by tumor thrombus because of the high risk of hepatic function insufficiency[30]. However, HCC growth mostly depends on 90% of the blood supply from the hepatic artery, whereas the normal liver parenchyma receives about 70% of its basic blood supply from the portal vein[31-33]. Based on this fact, TACE can provide a survival benefit to HCC patients by blocking the main nutrient vessels of tumor *via* an embolisation in the hepatic artery and subsequently allowing sustainable chemotherapeutic drugs to kill the HCC cells. This method is also effective in preventing compensatory circulation growth, reducing portal vein pressure and preventing intractable ascites and bleeding of esophageal varices[34-37]. Lee *et al*[38] reported that TACE is safe for the treatment of HCC with portal trunk obstruction when patients have sufficient collateral circulation around the portal trunk. Luo *et al*[18] showed that patients with major PVTT achieve better OS with TACE therapy than with conservative treatment. The 3-, 6-, 12- and 24-mo OS rates were 79.2%, 38.7%, 5.8% and 0% and 58.6%, 20%, 0% and 0%, respectively (P = 0.002). In our study, the survival rates (at 3, 6, 12 and 24 mo were 97.9%, 91.8%, 36.3%, 0.0% and 96.7%, 93.3%, 53.5%, 0.0%) and survival periods (10.22 mo *vs* 10.52 mo) increased mostly after TACE or TACE combined with sorafenib compared with other treatments.

TACE cannot completely block the nutrient transport to the tumor because of the small nutrient vessels from the portal vein; therefore, tumor necrosis is not completely achieved[18]. Generally, the cytotoxic effects of chemotherapy drugs follow log-cell kill kinetics, in which cells are killed proportionally. Therefore, tumor cells cannot be eliminated by one cycle of chemotherapy. With multiple treatment cycles, the possibility of killing residual tumor cells increases with enhanced prognosis[39]. Furthermore, among the patients with PVTT invading the main trunk of the portal vein, invisible intrahepatic metastasis is more likely to happen because the tumor cells were distributed *via* the portal vein system; in PVTT, these cells are located in a liver segment. Lipiodol can selectively accumulate in the invisible metastatic HCC when delivered intra-arterially and acts as a carrier for anticancer drugs. Hence, TACE can effectively block the nutrient vessels in the invisible metastatic HCC, thus allowing sustainable chemotherapeutic drugs to kill the microscopic HCC cells[35-37]. However, repeated TACE can damage the remnant liver parenchyma, particularly in cirrhotic patients, and result in liver function impairment or deterioration[40,41]. Thus, the number of TACE cycles should depend on the tumor response to TACE and patient's liver function.

Fortunately, patients who underwent TACE did not present serious adverse events or suffer from therapy-related death. Therefore, TACE should be considered a safe and effective treatment for HCC patients with PVTT extending to the main trunk and IVC.

Efficacy of sorafenib as an adjuvant treatment and single use of sorafenib

According to the BCLC group, the only recommended treatment for HCC patients with PVTT is sorafenib. Sorafenib is often used as an adjuvant therapy combined with TACE. As an oral small molecule tyrosine multikinase inhibitor of several intracellular proteins, sorafenib can intervene some factors regarding tumor progression, including the platelet derived growth factor receptor-β, Raf serine/threonine kinases and vascular endothelial growth factor receptor (VEGFR) receptors-1/2/3[42,43]. Sorafenib plays a critical role in tumor cell apoptosis and anti-angiogenesis of new born tumor, which further enhances the efficacy of TACE[44].

Basically, VEGF plays an important role in tumor recurrence and metastasis. Some reports[45,46] indicated that the VEGF level increases after TACE. Thus, anti-angiogenesis therapy *via* sorafenib is normally considered to contribute to preventing the development of new vessels supplying the tumor by suppressing the VEGFR level; consequently, the interaction between VEGF and VEGFR is decreased. Several studies[29,47,48] indicated that TACE combined with sorafenib would provide a better OS than single TACE. Several trials[49-51] also indicated that sorafenib used as a preoperative therapy would have benefit

Table 5 Factors affecting overall survival using Cox's proportional hazard model

Factor	Univariate analysis				Multivariate analysis		
	Patients, *n*	Mean OS (mo)	95%CI	*P* value	HR	95%CI	*P* value
Positive for HBsAg							
Yes	349	9.05	8.33-9.76	0.035	1.09	0.56-2.14	0.798
No	69	10.58	9.92-11.23				
Positive for anti-HCV							
Yes	19	6.00	2.49-9.51	0.026	1.45	0.44-3.88	0.454
No	399	9.42	8.90-9.94				
AFP (mg/L)							
> 400	134	7.99	6.94-9.05	< 0.001	1.84	1.09-3.11	0.023
≤ 400	284	9.96	9.42-10.49				
Child-Pugh Stage							
Stage A	262	9.88	9.34-10.42	< 0.001	1.99	1.20-3.30	0.008
Stage B	156	8.28	7.21-9.37				
Tumor size (cm)							
> 5	301	8.48	7.79-9.18	< 0.001	3.31	1.57-6.98	0.002
≤ 5	117	10.82	10.20-11.45				
Tumor number							
> 3	147	8.62	7.92-9.32	< 0.001	2.10	1.22-3.63	0.007
≤ 3	271	10.55	9.89-11.20				
Cirrhosis							
Yes	343	8.85	8.23-9.46	0.007	2.10	1.02-4.32	0.044
No	75	10.82	10.06-11.59				
Portal hypertension							
Yes	113	7.00	6.03-7.98	< 0.001	1.65	1.02-2.65	0.041
No	345	10.14	9.62-10.65				
Tumor thrombus location							
Main portal vein trunk	299	10.40	9.89-10.91	< 0.001	4.51	2.66-7.65	< 0.001
Inferior vena cava	119	4.83	4.26-5.41				

PVTT: Portal vein tumor thrombus; HBsAg: Hepatitis B surface antigen; anti-HCV: Hepatitis C virus antibody; PLT: Platelet count; TBil: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; AFP: Alpha-fetoprotein.

of shrinking the tumor size according to the response evaluation criteria in solid tumors and can downstage the HCC to undergo other therapies. However, the current study did not find that using sorafenib as an adjuvant therapy with TACE can significantly prolong the survival period compared with single TACE, probably because our study is basically focused on HCC patients with PVTT invading the main portal vein trunk or IVC, whereas the other studies emphasised on the patients without major PVTT or without PVTT. Similarly, a recent systematic review[50] evidenced that TACE combined with sorafenib would not prolong OS more than single TACE in unresectable HCC (HR = 0.81, 95%CI: 0.65-1.01, *P* = 0.061).

Nevertheless, single use of sorafenib would not provide a better survival benefit than palliative treatment. The survival rates at 3, 6, 12 and 24 mo were 50.9%, 29.5%, 0.0% and 0.0% in the single-use sorafenib group, respectively; correspondingly, these rates were 55.0%, 0.0%, 0.0% and 0.0% in the palliative group (*P* > 0.05). The survival period of the single-use sorafenib group (3.54 mo) was slightly longer than that of the palliative treatment group (2.82 mo). No obvious serious adverse events occurred in patients who used sorafenib. Nevertheless, for HCC patients associated with PVTT invading the main portal vein trunk, the single use of sorafenib as an adjuvant treatment can be recommended, but the efficacy remains under discussion.

Efficacy and safety of HR

PVTT is generally considered an absolute or related contradiction for surgery[52]. However, some studies[16,53] advocated that HR can achieve survival benefit and enhance life quality. Hepatectomy along the portal tributary is effective in eradicating the main gross tumor, tumor's surgical margins and possible satellite nodules; an embolectomy is feasible to remove the tumor thrombus from the portal vein system, consequently reducing portal vein pressure and allowing the recovery of blood flow in the portal vein; this method helps improve liver function and prevent the intractable ascites, bleeding of esophageal varices and its related death. In addition, the method reduces the tumor burden and increases the efficacy of postoperative multimodality treatments, such as TACE, hepatic artery infusion, portal vein infusion and biotherapy. Ban *et al*[22] indicated that hepatectomy and embolectomy to treat HCC with tumor thrombus extending to the main trunk of the portal vein can provide a comparable survival benefit similar to that achieved by hepatectomy for PVTT located in the first branch of portal vein or above. In the present study, HR was therefore considered an effective treatment method in selected HCC patients with PVTT involving the major portal vein. However, we cannot determine

a survival benefit after HR compared with other treatments, which is probably because the patients involved in our study were characterised with high exposure to HBV, chronic liver cirrhosis and PTH. These variables can lead to heavier damage of perioperative liver function and worse hepatic impairment after HR. When tumor thrombus extended to the main trunk of the portal vein, the risk of portal vein hypertension and its related diseases was increased, and the liver function damage was heavier than that in HCC without the obstruction by tumor thrombus in the major portal vein. Furthermore, HCC cells spread out and were distributed through the portal vein system, thereby leading to an invisible intrahepatic metastasis, which is the main mechanism of postoperative sustainable damage of residual liver function and recurrence. Thus, HR was no longer an eradicative treatment for HCC patients with PVTT invading the main trunk of portal vein. All of these variables affected the long-term survival of the patients. Similar to our finding, Peng *et al*[54] reported that compared with TACE, HR provides survival benefits for patients with resectable HCC with PVTT invading the portal vein branches but not the main portal vein trunk. Shi *et al*[16] proposed that hepatectomy and thrombectomy are viable treatments until the PVTT infiltrates into the main trunk of the portal vein. Nevertheless, in our study, complications and mortality in hospital after HR were most frequently comparable with those after other therapies. Overall, HR should be considered with precaution for HCC patients with PVTT invading the main trunk of the portal vein because it usually cannot prolong the OS but may increase the risk of postoperative complications and liver failure. Hence, the efficacy of the studied method remains controversial.

Prognostic factors for survival

Our multivariable analysis revealed that larger and multiple nodular HCCs were related to poor prognosis. This finding is not consistent with other reports indicating that tumor size larger than 10 cm and multiple nodules are not conflicting with HR. Moreover, HBV, cirrhosis and portal vein hypertension were identified as poor prognostic factors. The patients in our study came from the Guangxi Zhuang Autonomous Region of China, where the population shows the highest HBV-related HCC incidence rate worldwide[55,56]. Cirrhosis usually developed from the liver, which was repeatedly impaired by HBV, and consequently developed to PHT. Furthermore, among the patients in our study, PTH not only developed from chronic HBV and cirrhosis, but also from the blockage by tumor thrombus in the main trunk of the portal vein. Thus, the perioperative liver function of patients in our study suffered heavier damage than patients from other areas without HBV and PVT in the major portal vein. On the basis of bad damage of perioperative liver function, large and multinodular HCC tumors generally need major hepatic resection (such as left/right hemihepatectomy), which leads to longer operation period and more loss of blood compared with partial hepatectomy. This finding explains the aggravation of the impairment of postoperative liver function and increase of risk in postoperative liver failure and death in the hospital. Such reason also helps explain why the postoperative survival was poor in the current study. Furthermore, our study did not find the difference of survival in those patients until PVTT extended to the inferior vein cava compared with those patients whose PVTT had invaded the inferior vein cava.

The limitations of the present study include its retrospective nature. Moreover, patients were treated at a single centre. Another limitation is the characteristics of the HCC patients, who came from some geographic areas with the highest incidence of HCC[57]. Therefore, the study result may be specifically suitable for Asian population and focusing mainly on HCC. Further randomised controlled trials with large sample size are needed.

This retrospective study suggests the following for treatment of HCC patients with tumor thrombus invading the main trunk of the portal vein and IVC: (1) TACE provided the most significant survival benefit among other therapies without inducing serious adverse events. Thus, TACE should be recommended as a safe and effective therapy; (2) sorafenib as an adjuvant treatment and combined with TACE slightly prolonged the OS than single TACE. However, the single use of sorafenib did not obviously prolong the survival compared with palliative treatment. Therefore, sorafenib remains a good option as an adjuvant therapy, but the efficacy of its single use remains to be evaluated; and (3) although hepatic resection released the portal vein hypertension and its related disease, this method did not provide survival benefit but rather induced multiple complications and increased the risk of postoperative liver failure and related death. Thus, liver resection should be carefully selected, and the efficacy of this method remains controversial.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related death. Portal vein tumor thrombus (PVTT) was found invading the main trunk in 10%-15% patients with HCC. HCC patients with PVTT are generally considered to have lost the optimal opportunity to undergo transarterial chemoembolisation (TACE) and surgical intervention, and only sorafenib and palliative treatments are available. Studying the efficacy of TACE compared with surgical intervention and sorafenib for HCC with PVTT provides clinical significance for further application of this strategy to treat HCC.

Research frontiers

This study compared and evaluated the efficacy of four kinds of interventions for HCC patients with PVTT extending to the main portal vein. Results indicated

that only TACE with/without sorafenib provided a comparable survival benefit, whereas surgical intervention or sorafenib did not lead to better survival than palliative treatments.

Innovations and breakthroughs

This study revealed that for HCC patients with tumor thrombus extending to the main portal vein, TACE can yield a higher survival rate than surgical intervention or sorafenib.

Applications

This study evaluated the efficacy of TACE compared with surgical intervention and sorafenib treatment for HCC with PVTT. The results offered novel treatment choices for clinical surgeons to treat HCC patients with PVTT extending to the main portal vein.

Terminology

TACE is used for some patients with liver cancer that cannot be treated surgically or *via* radiofrequency ablation. TACE is also a minimally invasive technique to treat liver tumors, particularly HCC.

Peer-review

This study investigated the efficacy of TACE compared with surgical intervention and sorafenib for HCC patients with tumor thrombus extending to the main portal vein. The results are significant and applicable to clinical practices and studies.

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