Gamma Knife Radiosurgery Versus Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: a Propensity Score Matching Study

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Research Article

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Abstract

Background

The optimal management for hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) is unclear. This study aimed to investigate the efficacy of Gamma knife radiosurgery (GKR) versus transcatheter arterial chemoembolization (TACE) in HCC patients with PVTT.

Methods

This retrospective study included 572 HCC patients with PVTT (GKR, 207; TACE, 365). Propensity score matching (PSM) analysis identified 188 matched pairs of patients. The primary endpoint was overall survival (OS).

Results

Before PSM, the GKR group demonstrated significantly median OS (mOS) than TACE group (17.4 vs. 8.0 months, $p < 0.001$). In the subgroup analysis, GKR was associated with significantly longer OS for patients with PVTT II-IV (17.5 vs. 8.2 months, $p < 0.001$; 19.3 vs. 7.4 months, $p < 0.001$; 14.5 vs. 6.6 months, $p = 0.008$, respectively) and comparable OS for patients with PVTT I. After PSM, the GKR group had also a longer OS (mOS) than TACE group (15.8 vs. 9.8 months, $p < 0.001$). In the subgroup analysis, the GKR group demonstrated superior mOS for patients with PVTT II-IV (all $P < 0.05$) and comparable OS for patients with PVTT I.

Conclusions

GKR was associated better OS than TACE in HCC patients with PVTT, especially for patients with PVTT II-IV.

Introduction

Hepatocellular carcinoma (HCC) is characterized by high morbidity and death (1). HCC is prone to invade the portal vein system and can cause portal vein tumor thrombus (PVTT), which is a poor prognostic factor and results in a median overall survival (mOS) of only 2-4 months (2–4). According to current literature, liver resection (LR) is the preferred treatment in PVTT I/II patients with Child-Pugh A and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1 (5, 6). However, for patients with other types of PVTT, there is still controversy regarding the best therapeutic approaches (7).

With the advancement of local therapeutic techniques, extremely transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), radiotherapy including gamma knife radiosurgery (GKR) and stereotactic body radiation therapy (SBRT) have become feasible. HCC patients with PVTT receiving TACE extended months mOS to 4-10 months (8, 9). But as an invasive treatment, TACE has a great impact on the life of the patient and carries risks such as liver failure. GKR is a form of

external radiotherapy, it can allow delivery of ablative doses of radiation with low toxicity. A retrospective study of small sample of patients reported that the mOS of HCC patients with PVTT who received GKR was 6.1 months (95%CI: 4.7-7.5) (10). In addition, a study by Xiaojie and colleagues reported that patients with HCC-derived PVTT who received GKR combined with TACE had longer OS than those treated with TACE alone (11).

Although HCC patients with PVTT who do not undergo surgery are candidates for both GKR and TACE, to the best of our knowledge, no data comparing these modalities is available. Therefore, we conducted this study to compare the effectiveness of GKR versus TACE for HCC patients with PVTT.

Materials And Methods

Patients

This is a multicentre, retrospective, cohort analysis of HCC patients with PVTT treated with GKR or TACE between June, 2015 and July, 2021.

The inclusion criteria were as follows: (1) patients aged 18 years or older; (2) histological or cytological diagnosis of HCC; (3) confirmation of PVTT by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI); (4) measurable lesions assessed as per Response Evaluation Criteria in Solid Tumors RECIST Version 1.1 (RECIST 1.1); (5) Child-Pugh class of A or B; (6) score of 0 to 1 according to ECOG PS; (7) tumor surgery deemed unfeasible, difficult, or unsuitable.

The exclusion criteria were as follows: (1) patients concomitantly received other treatments such as sorafenib, TACE plus GKR, hepatic resection, or radiofrequency ablation; (2) patients with obstinate ascites, hepatic encephalopathy; (3) patients with cancers other than HCC; (4) inadequate clinical data; (5) patients who had used any treatment of anti-tumor within 12 weeks prior to the first treatment in this study.

Classification of PVTT

We followed the Cheng's classification for PVTT and classified the types of PVTT according to four levels: (a) type I was defined as PVTT in the segmental or sectoral branches of the portal vein or above; (b) type II was defined as PVTT in the right/left portal vein; (c) type III was defined as PVTT in the main portal vein; and (d) type IV was defined as PVTT in the superior mesenteric vein. Type I0 represented tumor thrombus found only under microscopy observation (12-14).

Treatment Protocol

The decision to offer GKR, TACE for HCC was made by the Hospital HCC Expert Team including hepatologists, radiation oncologists, surgeons, interventional radiologists, medical oncologists and pathologists. All patients signed informed consents before they received any treatment.

GKR

GKR was performed using Treatment Planning System (TPS) by two or three radiation oncologists who delineated the irradiation area as per contrast-enhanced CT scan. Delineation of the gross target volume (GTV) including the primary liver tumor and tumor thrombosis was done based on the image technology. The radiation oncologists defined a 5-10 mm margin around the GTV as the planning target volume (PTV) by TPS. The median tumor margin dose was 42 Gy (range, 39 to 42 Gy), with a median isodose line of 50% (range, 50% to 60%). Dose-volume histograms were used to protect adjacent normal tissues and the liver, as delineated during the target planning process. The course of GKR treatment was divided into 2 cycles with 7 times per course (once a day). The radiation oncologists revised the treatment plan by CT after the first course of treatment, and ahead of the second course of treatment.

TACE

TACE was performed by delivering an emulsion of lipiodol (10-20 ml) and one or more chemotherapeutic agents, such as cisplatin, or cisplatin and mitomycin-C, or Fluorouracil. The delivery was performed into the selected vessels after a microcatheter was advanced into the hepatic arterial circulation to the most distal tumor-feeding vessel, followed by embolization using gelatin sponge particles or other embolic materials if deemed necessary.

Repeated TACE procedures were performed in the case of multiple lesions or large lesions. The decision to perform multiple TACE was made by HCC Expert Team.

Patient Follow-Up and Data Collection

Post-treatment follow-ups were conducted every 2-3 months and entailed comparison of CT, or MRI and laboratory tests at baseline. Laboratory tests included biochemical and hematologic analyses, such as pro-thrombin time; complete blood cell count; and measurements of α -fetoprotein (AFP), total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels. Patients with recurrent tumor on CT or MRI images underwent second-line treatment.

Statistical Analysis

Categorical variables were analyzed using χ^2 and McNemar analysis. One-to-one propensity score matching (PSM) was adopted to reduce selection bias and confounding factors resulting from different co-variable distribution among GKR and TACE groups. Independent variables included in the propensity model were sex, age, Child-Pugh classification, tumor number, tumor size, AFP levels, ALP levels, platelet levels, ALT levels, leukocyte levels, type of PVTT, HBV infection, HCV infection, drinking history, lymph node metastasis, extrahepatic metastasis, and previous therapy status. Survival was computed as the interval between the date of GKR or TACE and the date of death for any reason, with censoring at the date of last follow-up in surviving patients. Kaplan–Meier method with log-rank test was utilized to compare long-term survival distribution. In exploratory subgroup analyses, the OS of GKR and TACE in predefined subgroups was assessed using Cox proportional hazard models presented in a forest plot; forest plots

show factors associated with OS. Univariate and multivariable Cox analyses of all data were done to confirm significant predictors for OS. Factors with P values less than 0.05 in univariate analysis were introduced into the multivariate Cox proportional hazards model to determine the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted with SPSS for Windows (version 26.0). Two tailed P value ≤ 0.05 were considered as statistically significant.

Results

Patient characteristics of the pooled and matched cohorts

Between June, 2015 and July, 2021, 4563 patients were diagnosed with HCC. Among them, 3991 patients did not meet the eligibility criteria and were excluded. We included in this study 207 patients who received GKR and 365 patients who received TACE (**Supplementary Fig. 1**). Before matching, the median follow-up period was 25.5 months (95% CI 19.1–31.9) for the GKR group and 20.8 months (95% CI 17.8–23.8) for the TACE group. Patients who underwent TACE had more multiple tumors ($P = 0.012$), larger tumors ($P = 0.007$), higher AFP levels ($P = 0.001$), more lymph node metastases ($P = 0.010$), worse PVT type ($P = 0.016$) than did those patients who underwent GKR. Patients in the GKR group had experienced a higher number of previous therapies ($P < 0.001$) than patients in the TACE group (Table 1).

Table 1
Baseline characteristics of the patients before and after PSM

	Before PSM			After PSM		
Variable	GKR	TACE	P	GKR	TACE	P
patients	207	365		188	188	
Male sex	183(88.4)	320(87.7)	0.795	164(87.2)	170(90.4)	0.405
Age $\geq$ 60 years	77(37.2)	117(32.1)	0.212	65(34.6)	70(37.2)	0.630
Child–Pugh B	59(28.5)	116(31.8)	0.414	56(29.8)	60(31.9)	0.724
Number of tumors $\geq$ 2	155(74.9)	305(83.6)	0.012	147(78.2)	157(83.5)	0.220
Tumor size $\geq$ 5 cm	151(72.9)	301(82.5)	0.007	142(75.5)	155(82.4)	0.085
Serum AFP $\geq$ 400 ng/ml	97(46.9)	223(61.1)	0.001	95(50.5)	108(57.4)	0.154
ALP levels $\geq$ 125 U/L	135(65.2)	270(74.0)	0.027	127(67.6)	133(70.7)	0.556
Platelet count $\geq$ 100 $\times$ 10 ⁹ /L	153(73.9)	267(73.2)	0.843	139(73.9)	133(70.7)	0.550
ALT levels $\geq$ 40 U/L	122(58.9)	227(62.2)	0.443	112(59.6)	112(59.6)	1.000
leukocyte $\geq$ 4 $\times$ 10 ⁹ /L	163(78.7)	292(80.0)	0.720	151(80.3)	151(80.3)	1.000
Number of TACE $\geq$ 2	-	80(21.9)		-	40(21.3)	
Cheng's type of PVTT			0.016			0.139
I	44(21.3)	45(12.3)		35(18.6)	29(15.4)	
II	63(30.4)	147(40.3)		58(30.9)	78(41.5)	
III	67(32.4)	118(32.3)		62(33.0)	55(29.3)	
IV	33(15.9)	55(15.1)		33(17.6)	26(13.8)	
Etiology						
HBV	138(66.7)	221(60.5)	0.146	123(65.4)	118(62.8)	0.649
HCV	4(1.9)	9(2.5)	0.681	4(2.1)	4(2.1)	1.000
Alcohol	89(43)	147(40.3)	0.525	81(43.1)	76(40.4)	0.691
Lymph node metastasis	103(49.8)	222(60.8)	0.010	93(49.5)	104(55.3)	0.289
Extrahepatic metastases	58(28.0)	102(27.9)	0.985	48(25.5)	57(30.3)	0.368
Lung	29(14.0)	71(19.5)		25(13.3)	40(21.3)	
Bone	24(11.6)	17(4.7)		16(8.5)	8(4.3)	

	Before PSM			After PSM		
other	19(9.2)	28(7.7)		17(9.0)	17(9.0)	
Previous therapy	102(49.3)	74(20.3)	<0.001	85(45.2)	73(38.8)	0.210
Systemic therapy	45(21.7)	9(2.5)		40(21.3)	9(4.8)	
Liver resection	44(21.3)	24(6.6)		34(18.1)	23(12.2)	
radiotherapy	18(8.7)	0		14(7.4)	0	
TACE	51(24.6)	51(14.0)		39(20.7)	51(27.1)	
RFA	14(6.8)	4(1.1)		11(5.9)	4(2.1)	
Abbreviations: PSM, propensity score matching; AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; PVTT, portal vein tumor thrombus; HBV, hepatitis B virus; HCV, hepatitis C virus; GKR, gamma knife radiosurgery; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.						

After performing PSM, we identified 188 matched pairs of patients with comparable patient and tumor characteristics. In this matched cohort, patients in the GKR and TACE groups were not significantly different with regards to any patient or tumor covariates at baseline (Table 1). The median follow-up time was 25.9 months (95% CI 20.2-31.6) in the GKR group and 20.8 months (95% CI 13.7-27.9) in the TACE group.

Overall Survival Analyses in the pooled and matched Cohorts

At the cutoff date (September 1, 2021), In the pooled cohort, 105 patients (50.7%) in the GKR group and 253 (69.3%) in the TACE group had died. The mOS was 17.4 months (14.2-20.6) in the GKR group and 8.0 months (6.4-9.6) in the TACE group ($p < 0.001$, Fig. 1A). The cumulative OS rates at 12, 18, and 24 months were 62.9%, 46.1%, and 40.4% in the GKR group, and 39.3%, 30.7%, and 25.2% in the TACE group, respectively. The OS rates were significantly higher in patients in the GKR group than in those in the TACE group ($p < 0.001$). In subgroup analysis according to the type of PVTT, patients in the GKR group had a significantly longer OS than those patients with PVTT type II, III and IV in the TACE group (17.5 vs. 8.2 months, $p < 0.001$, Fig. 2C; 19.3 vs. 7.4 months, $p < 0.001$, Fig. 2E; 14.5 vs. 6.6 months, $p = 0.008$, Fig. 2G; respectively). However, there was no significant difference in the OS between the two groups of patients with PVTT type I (14.4 vs. 12.5 months, $p = 0.396$, Fig. 2A).

In the matched cohort, 102 (54.3%) patients in the GKR group patients and 126 (67.0%) in the TACE group patients died. The GKR group had a mOS of 15.8 (13.4–18.2) months, which was higher than that of 9.8 (6.1–13.5) months in the TACE group ($p < 0.001$, Fig. 1B). The cumulative OS rates at 12, 18, and 24 months were 59.7%, 41.9%, and 36.8 in the GKR group, and 45.1%, 34.8%, and 27.4% in the TACE group ($p < 0.001$), respectively. Patients with PVTT type II, III and IV in the GKR group had also a significantly

longer OS than their counterparts the TACE group (17.5 vs. 9.8 months, $p = 0.003$, Fig. 2D; 17.2 vs. 7.8 months, $p = 0.028$, Fig. 2F; 14.5 vs. 5.5 months, $p = 0.043$, Fig. 2H; respectively). There was no significant difference in the OS between the two groups of patients with PVTT type I (11.2 vs. 14.4 months, $p = 0.703$, Fig. 2B).

Exploratory subgroup analysis of associated factors in the matched Cohorts

In exploratory subgroup analyses of OS after PSM (**Supplementary Fig. 2**), GKR seemed most beneficial in male patients ($p = 0.002$); those younger than 60 years ($p = 0.001$); tumor size ≥ 5 cm ($p = 0.002$); ALP ≥ 125 U/L ($P < 0.001$); ALT ≥ 40 U/L ($P < 0.001$); leukocyte $\geq 4000/\mu\text{L}$ ($p = 0.002$); PVTT type II-IV ($p = 0.003$, $p = 0.030$, $p = 0.048$, respectively); non-HCV ($p = 0.001$); non-lymh node metastases ($p < 0.001$); and non-extrahepatic metastases ($p < 0.001$).

Factors Associated with Overall Survival in the matched Cohorts

We performed univariate and multivariate Cox regression analyses to confirm prognostic independent factors after PSM. The child A, GKR, number of tumors < 2 , tumor diameter < 5 cm, and ALP < 125 U/L were all confirmed as independent positive prognostic factor for OS (all $p < 0.005$, Table 2).

Table 2
univariate and multivariate Cox regression analysis of overall survival after PSM

Variable	Univariable Cox regression			Multivariable Cox regression		
	HR	95%CI	P	HR	95%CI	P
Sex (male/female)	1.004	0.667-1.511	0.984			
Age (≥ 60 / <60 years)	0.813	0.617-1.072	0.143			
Child-Pugh class (B/A)	1.657	1.256-2.184	<0.001	1.426	1.074-1.894	0.014
Number of tumor (≥ 2 / <2)	1.780	1.235-2.566	0.002	1.497	1.035-2.164	0.032
Tumor diameter (≥ 5 / <5 cm)	2.282	1.563-3.329	<0.001	1.896	1.292-2.781	0.001
AFP (≥ 400 / <400 ng/ml)	1.266	0.973-1.646	0.079			
ALP (≥ 125 / <125 U/L)	1.95	1.439-2.644	<0.001	1.642	1.194-2.258	0.002
Platelet (<100000 / ≥ 100000 / μ L)	1.267	0.938-1.713	0.123			
ALT (≥ 40 / <40 U/L)	1.223	0.936-1.597	0.14			
leukocyte (<4000 / ≥ 4000 / μ L)	1.14	0.818-1.59	0.439			
Cheng's type of PVTT			0.641			
I	1.000					
II	1.045	0.710-1.538	0.825			
III	1.149	0.776-1.703	0.488			
IV	1.294	0.824-2.030	0.263			
HBV (positive/negative)	1.199	0.911-1.578	0.195			
HCV (positive/negative)	1.166	0.549-2.476	0.689			
Alcoholism (positive/negative)	0.963	0.740-1.254	0.782			

	Univariable Cox regression			Multivariable Cox regression		
Lymph node metastasis (yes/no)	1.21	0.931-1.572	0.153			
Extrahepatic metastases (yes/no)	1.264	0.954-1.675	0.103			
Previous therapy (yes/no)	0.939	0.722-1.222	0.641			
Treatment (GKR/TACE)	0.628	0.484-0.816	<0.001	0.664	0.510-0.864	0.002
Abbreviations: PSM, propensity score matching; HR, hazard ratio; PVTT, portal vein tumor thrombus; AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; GKR, gamma knife radiosurgery; TACE, transcatheter arterial chemoembolization.						

Discussion

To the best of our knowledge, this is the first study to investigate the efficacy of GKR vs. TACE monotherapy in the treatment of HCC-PVTT patients. Treatment options are limited for HCC patients with PVTT, according to the NCCN guidelines (15). Previous studies reported that LR is the preferred treatment in PVTT I/II patients with good liver function but first-line treatment remains controversial in PVTT III/IV (5–7).

In this study, the TACE group had heavier tumor burden and higher AFP levels than the GKR group before PSM. Therefore, we performed PSM to reduce bias due to confounding in baseline characteristics between the two groups. We found that GKR was superior to TACE with respect to the survival time for patients with PVTT II, III, and IV (all $P < 0.05$). However, no significant difference in the OS before and after PSM was observed for patients with PVTT I. These results have implications for the treatment of HCC patients with PVTT.

Although both GKR and TACE are local therapies to induce tumor cell death, the two modalities differ substantially in their principles and processes of treatment, which might be underlie differences in treatment efficacy in HCC. A growing number of studies reported that TACE can be safely conducted in patients with incomplete obstruction of the main portal vein or formation of abundant compensatory collateral branches of the portal vein, or recanalized portal vein by portal vein stenting despite complete obstruction (16–19). However, in cases of complete obstruction of the main portal vein by tumor thrombi with few collateral branches formed, TACE is contraindicated (16). Patients with PVTT type II, III, and IV often experience severe obstruction of the portal vein, which might be associated with the poor survival time of these patients in the TACE. In contrast, GKR, an external RT method, is the most widely used form of stereotactic radiosurgery in the USA due to its precision and the efficiency of radiation delivered in a single session (20, 21). With development of RT technology, radiation dosage of targeted regions can be increased while achieving protection of the adjacent healthy tissues, thereby making it suitable for HCC

patients with all types of PVTT (7, 22, 23). In addition to sustaining local control with low toxicity, local RT also induce immunogenic cell death, increase the release of tumor antigens and activate the immune system (10, 24–26).

It is still unclear what the best therapeutic options for HCC patients with PVTT are. A retrospective study reported that HCC patients with PVTT who received GKR plus TACE had longer OS than those who received TACE alone (9.7 vs. 6.2 months, respectively; $p < 0.001$) (11). A study by Li and colleagues reported that mOS values of 8 vs. 10 months in the intensity-modulated radiation therapy (IMRT) and SBRT groups ($p = 0.165$) (27). In addition, Silva et al. conducted a meta-analysis and reported that the mOS of HCC patients who received TACE was 8 months (19). In our study, patients in the GKR group experienced longer survival time than those in the TACE after PSM (15.8 vs. 9.8 months, $p < 0.001$). At the same time, it is important to note that the total cost of GKR and TACE alone are similar in China. And due to non-invasion of GKR, patients are more willing to accept the GKR rather than TACE. In summary, taking into consideration overall efficacy and costs, GKR appears to be a more feasible therapeutic option for HCC patients with PVTT.

Next, we explored the prognostic factors for HCC patients with PVTT and found that GKR was independently associated with long-term OS. In addition, the presence of multiple tumors, tumor diameter ≥ 5 cm, ALP ≥ 125 U/L and Child B were associated with inferior OS after PSM. These findings are in line with previous reports linking these factors with poor prognosis in HCC patients (28–30).

This study has several limitations. Firstly, this was a retrospective study and as such it is prone to potential bias. We conducted PSM to avoid selection bias, but we cannot exclude potential confounding factors. Secondly, the information on the adverse effects was limited. Finally, the sample size of the GKR group was relatively small, although our study had the largest HCC patients with PVTT ever reported to our knowledge.

Conclusions

In conclusion, in this multicenter retrospective study, GKR showed better OS than TACE in HCC patients with PVTT, especially in those with PVTT type II, III and IV. These findings have significant implications for the treatment of HCC patients with PVTT. Prospective randomized trials are needed to demonstrate potential benefit and safety of GKR.

Declarations

Funding support

None.

Competing Interests

The authors declare no conflict of interest regarding the content of this paper.

Author Contributions

Ke Su, Tao Gu, Ke Xu, Jing Wang, Hongfei Liao, Xueting Li, Lianbin Wen, Yanqiong Song, Jiaqi Zhong, Bingsheng He, Xin Liu, Jie He, Yanlin Liu, Qi Li, Xunjie Feng, Siyu Chen, Binbin Yang, Weihong Huang, Hongping Jin, Xiaotong Luo, Teng Hu, Jiali Chen, Zhenying Wu, Simin Lu, Jianwen Zhang, Mingyue Rao, Yunchuan Xie, Jing Wang, Xiaoning Zhu, Lan Chen, Bo Li, Song Su, Xiaoli Yang, Juan Wang, Hao Zeng, Pan Wang, Xiaojing Chen, and Min Yan collected the data. Yunwei Han and Kun He designed the research study. Ke Su, Tao Gu, Ke Xu, Kun He and Yunwei Han wrote the manuscript and analyzed the data. All authors approved the final version of the manuscript.

Data Availability

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author (Lanpaoxiansheng@126.com).

Animal Research (Ethics)

This research did not involve animal experiments.

Consent to Participate (Ethics)

This retrospective study was approved by the Ethics Committee of The Affiliated Hospital of Southwest Medical University (approval number KY2020254) and complied with the standards of the Declaration of Helsinki. Written informed consent was waived because of the retrospective study.

Consent to Publish (Ethics)

The all authors confirmed that the work described has not been published before and it is not under consideration for publication elsewhere. Its publication has been approved by all co-authors and the Affiliated Hospital of Southwest Medical University.

Plant Reproducibility

None.

Clinical Trials Registration

The study was registered in the Chinese Clinical Trials Registry under the registration number ChiCTR2100051057

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Figures

Figure 1

(A) GKR had significantly improved overall survival compared to TACE before propensity score matching (17.4 vs. 8.0 months). (B) GKR had significantly improved overall survival compared to TACE in the matched cohort (15.8 vs. 9.8 months). Abbreviations: GKR, gamma knife radiosurgery; TACE, transcatheter arterial chemoembolization.

Figure 2

Overall survival curves for the patients with portal vein tumor thrombus (PVTT) type I (A), II (C), III (E), and IV (G) who received GKR and TACE are shown before propensity score matching. Overall survival curves for the patients with portal vein tumor thrombus (PVTT) type I (B), II (D), III (F), and IV (H) who received GKR and TACE are shown after propensity score matching. Abbreviations: GKR, gamma knife radiosurgery; TACE, transcatheter arterial chemoembolization.

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