Original Article

Liver resection versus intensity-modulated radiation therapy for treatment of hepatocellular carcinoma with hepatic vein tumor thrombus: a propensity score matching analysis

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Background: The presence of hepatic vein tumor thrombus (HVTT) is a major determinant of survival outcomes in hepatocellular carcinoma (HCC) patients. This study compared survival outcomes between liver resection (LR) and intensity-modulated radiation therapy (IMRT) in HCC patients with HVTT.

Methods: Data from patients who underwent LR or IMRT for HCC with HVTT at the Eastern Hepatobiliary Surgery Hospital were retrospectively analyzed. Their survival outcomes were compared before and after propensity score matching (PSM).

Results: Three hundred and seven HCC patients with HVTT who underwent either LR (n=140) or IMRT (n=167) were enrolled. PSM matched 82 pairs of patients. The overall survival (OS) and recurrence-free survival (RFS) rates were significantly higher for patients in the LR group than those in the IMRT group. On subgroup analysis, significantly better survival outcomes were obtained after LR than IMRT in patients with peripheral type of HVTT (pHVTT) and major type of HVTT (mHVTT). However, similar survival outcomes were obtained after LR and IMRT when the HVTT had developed into inferior vena cava tumor thrombus (IVCTT).

Conclusions: LR resulted in significantly better survival outcomes in HCC patients with HVTT when compared to IMRT. Once the HVTT had developed IVCTT, LR and IMRT resulted in similarly bad survival outcomes.

Keywords: Hepatocellular carcinoma (HCC); hepatic vein tumor thrombus (HVTT); liver resection (LR); radiotherapy

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death globally (1). HCC often invades macrovascular lumens such as the portal or hepatic venous branches to form a portal vein tumor thrombus (PVTT) or a

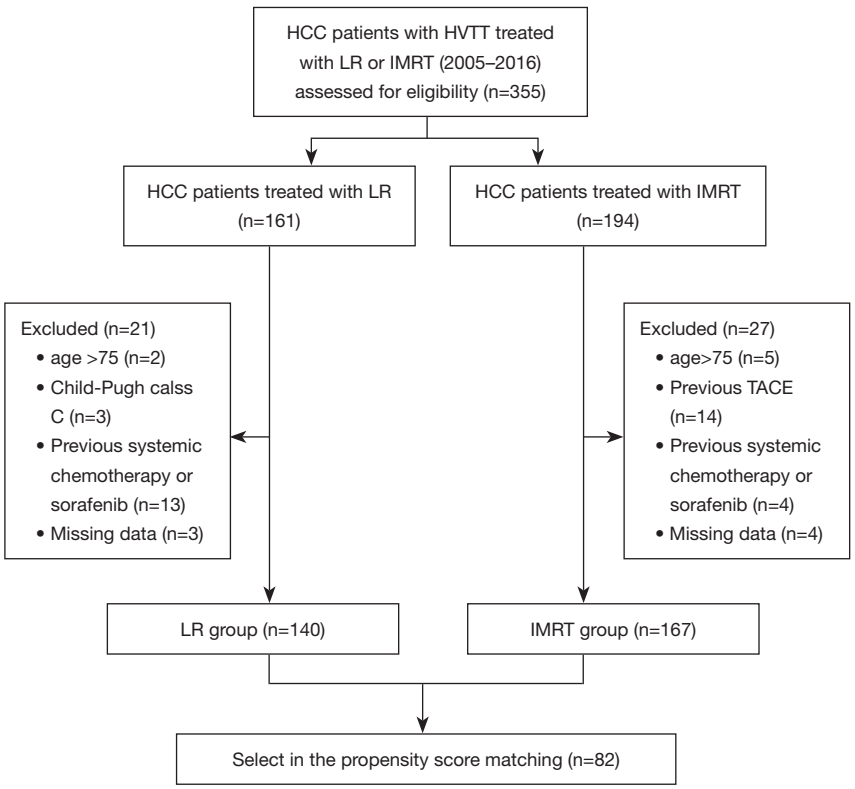

Figure 1 Flowchart of screening all HCC patients with HVTT for the study. HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; IMRT, intensity-modulated radiation therapy; LR, liver resection.

hepatic vein tumor thrombus (HVTT). The incidences of PVTT or HVTT have been reported to range in patients with HCC from 44% to 62.2% or from 1.4% to 4.9%, respectively (2-4). Either PVTT or HVTT is a known significant risk factor affecting long-term survival for HCC patients (3,5). Knowledge on HVTT is especially limited due to its low incidence. Invasion and extension of HVTT to the inferior vena cava (IVC) and right atrium (RA) can cause sudden death due to heart failure or massive pulmonary embolism (6). The best treatment strategy for HCC patients with HVTT remains controversial. The Barcelona Clinic for Liver Cancer (BCLC) Staging System and Treatment Guidelines consider presence of HVTT or PVTT to be at an advanced stage of HCC, with almost zero hope for a cure. Sorafenib is recommended as the only treatment option (7,8). A phase III randomized controlled trial reported a median survival time (MST) of only 6.5 months for these patients (7). Furthermore, recent studies from Asia showed that liver resection (LR) can result in better survival outcomes compared to nonsurgical treatment in selected HCC patients with HVTT (3,9-11).

Improvements in radiation therapy (RT) which include image-guided radiation therapy (IGRT) and intensity-modulated radiation therapy (IMRT) have allowed increasing use of external RT in treatment of HCC. Retrospective and prospective studies have showed RT to be safe and effective in patients with advanced and unresectable HCC (12-14) or with macroscopic portal/hepatic venous invasion (15-17). Furthermore, RT can be given as an outpatient basis, and it seldom produces grade 3 or higher liver, gastrointestinal, or hematological toxicities (18,19).

In this large-scale retrospective study, the long-term survival outcomes of HCC patients with HVTT who underwent LR or IMRT as their primary treatments were analyzed. To minimize potential biases which are inherent to retrospective studies, propensity score matching (PSM) analysis was used to determine the differences in long-term survival outcomes between these two treatments.

We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.20/rc).

Methods

Patients enrollment

As shown in *Figure 1*, 355 consecutive HCC patients with HVTT who underwent LR or IMRT as primary treatments at the Eastern Hepatobiliary Surgery Hospital from January 2005 to December 2016 were included in this study. Forty-eight patients were excluded from the study because they met the exclusion criteria. Thus, 307 patients (LR group, n=140; IMRT group, n=167) formed the basis of this study. After PSM with a 1:1 ratio matching, there were 82 patients in each of the LR and the IMRT groups. The demographic, clinical and pathological data, and survival outcomes were recorded prospectively in a HCC database and analyzed retrospectively. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the Eastern Hepatobiliary Surgery Hospital (Permit Number: HBHKY-2019-001-017). Informed consent was obtained from all the patients prior to treatment.

The extent of HVTT was categorized as: a tumor thrombous in a peripheral hepatic vein precluding the microscopic HVTT (pHVTT), in a major hepatic vein (mHVTT), or in the inferior vena cava (IVCTT) (3). In HCC patients who had HVTT coexisting with PVTT, the extent of PVTT was classified according to the Cheng's classification of the extent of PVTT in the portal vein (20): Type I, tumor thrombus in the segmental branches of the portal venous system or above; Type II, tumor thrombus extending to the right or the left portal vein; Type III, tumor thrombus extending to the main portal vein; and Type IV, tumor thrombus extending to the main portal vein and the superior mesenteric vein.

Inclusion and exclusion criteria

The presence of HVTT and PVTT was identified by preoperative Doppler ultrasonography, enhanced computed tomography (CT) or magnetic resonance image (MRI), and was later confirmed by final histopathological examination in the group of patients who underwent LR.

The inclusion criteria for surgery group were: (I) age between 18 and 75 years; (II) HCC patients who underwent LR as the primary treatment; (III) liver function of Child-Pugh class A or selected B (score ≤7); (IV) MELD score <11; and (V) resectable HCC which was defined as HCC which the potential to be completely removed of all macroscopic tumor tissues and with a future liver remnant of a volume sufficient to sustain life after surgery as assessed by our surgical team (21). The MELD score was 7.9±2.1 for the surgery group, and 8.4±2.5 for the IMRT group. There were 53 (37.9%) patients underwent TACE and 13 (9.3%) patients underwent sorafenib along with LR (n=140).

The exclusion criteria were: (I) Liver function of Child-Pugh class C; (II) underwent preoperative anti-cancer treatment which included sorafenib, radiofrequency ablation, TACE, and/or ethanol injection; (III) presence of distant metastases; and (IV) incomplete data.

LR

LR was performed as previously reported by us (22). Only patients with liver functions of Child-Pugh A or selected B were offered surgery. After exploration, routine intraoperative ultrasonography was carried out to determine the location and extent of HVTT, IVCTT, PVTT, and to rule out any preoperatively undetected tumors in the future liver remnant. The abdominal cavity was carefully searched for the extent of local disease, extrahepatic metastases, and peritoneal seeding. For patients with a tumor thrombus in a portal vein, the blood inflow of the liver was occluded using the Pringle's maneuver at a site distal to the thrombus. The clamp crushing method was used to carry out liver transection. Anatomical LR with *en bloc* thrombectomy was our preferred surgical method. As an alternative, non-anatomical resection was used in patients when *en bloc* resection was not technically feasible. For PVTT, thrombectomy was performed according to the types of PVTT. For patients with Type I or II PVTT, the PVTT was resected *en bloc* with the specimen (22). After flushing with normal saline and confirmation with intraoperative ultrasonography that no tumor thrombus remained, the vascular incision was closed with a continuous suture. For HVTT, the tumor thrombus was either resected *en bloc* with the LR or it was extracted out of the vascular lumen depending on its location and extent. For HVTT with a tumor thrombus extending to the IVC, the infrahepatic and suprahepatic IVC were exposed and encircled with umbilical tapes for total hepatic vascular exclusion (THVE). Before the initiation of THVE, test clamping of the IVC was repeated several times to determine whether a

venovenous bypass was necessary. During THVE, the patient's hemodynamic condition was carefully monitored and aggressively treated by the anesthesiology team. In patients with an IVC tumor thrombus extending above the diaphragm, the supradiaphragmatic IVC was dissected by blunt and sharp dissections through a vertical incision in the diaphragm (23). The supradiaphragmatic IVC was then encircled and controlled by a tape. When an IVC tumor thrombus had extended into the RA, a median sternotomy was made, and cannulations of the ascending aorta, superior vena cava, and right femoral vein were carried out to perform extracorporeal circulation (ECC).

IMRT

IMRT was performed in patients who were not eligible to undergo LR because of inoperable tumors. Some patients preferred IMRT because of the surgery refusal. The inclusion criteria were: (I) age between 18 and 75 years; (II) HCC patients who underwent IMRT as the primary treatment; (III) liver function of Child-Pugh class A or selected B (score ≤7); (IV) absence distant metastases. The MELD score was 8.4±2.5 for the IMRT group. There were 65 (38.9%) patients underwent TACE, 18 (10.8%) patients underwent sorafenib along with IMRT (n=167). A computed tomographic scan was performed with the patient in a supine position, with thermoplastic mask immobilization to reduce setup uncertainty and to restrain liver motion caused by abdominal breathing. Preoperative MRI scans were used to optimize target and normal structure delineation. The clinical target volume (CTV) included the primary tumor and tumor thrombus. Considering respiratory liver motion and setup errors in four-dimensional (4D) CT, the planning target volume (PTV) was defined by expanding the CTV by 0.5 cm in the anterior-posterior and left-right directions and by 1.0 cm in the cranial-caudal direction. IMRT plans were then generated for each patient. In all patients, the goal was for at least 95% of the clinical treatment volume to receive 100% of the dose. The plans were optimized independently and reviewed by at least a dosimetrist and a physicist. The prescribed doses to the initial PTV ranged from 50 to 67 Gy (median 58 Gy), given in daily doses of 2.0–2.2 Gy. The biologically effective dose (BED) ranged from 61.0 to 82.5 Gy (median 68.2 Gy, $\alpha/\beta=10$). The dose was selected so as not to cause too much damage to the vascular components near the HVTT, which would result in postoperative complications

Follow-up

Patients were followed-up once every 3 to 4 months until death or dropout from the follow-up program. Follow-up examinations were conducted using laboratory tests (serum AFP, liver function and complete blood count), abdominal ultrasonography and contrast-enhanced CT. A diagnosis of HCC recurrence was based on CT and/or magnetic resonance imaging with or without a raised serum α-fetoprotein (AFP) level. Patients with recurrence or metastasis were treated by TACE, radiofrequency ablation therapy, hepatectomy, systemic chemotherapy, or sorafenib therapy. Therapy was decided based on hepatic function, performance status, and economic conditions. Overall survival (OS) was defined as the interval between operation/IMRT and death due to any cause or the last follow-up. Recurrence-free survival (RFS) was defined as the interval from the date between operation/IMRT to the date when HCC recurrence was diagnosed. OS and RFS were the primary outcomes of this study. This study was censored on May 1, 2018.

Statistical analysis

For comparisons between baseline variables, the Wilcoxon rank-sum test was used for continuous variables and the chi-squared test for categorical variables. Survival curves were conducted using the Kaplan-Meier method, and the differences were analyzed using the log-rank test. Prognostic factors found to be significant on univariate analysis ($P<0.05$) were subjected to multivariate analysis using the Cox proportional hazards regression model. The PSM method was used to control selection bias and to create demographically and clinically comparable cohorts. The propensity score was estimated using the non-parsimonious multivariate logistic regression according to age, sex, Child-Pugh class, hepatitis B virus infection, satellite nodules, AFP, CEA, CA-19.9, tumor diameter, tumor number, extent of PVTT, and extent of HVTT. Patients were matched at a 1:1 ratio using the caliper matching method within 0.2 of the standard deviation of the logit of the PS. Statistical analyses were performed using the R statistical package, Version 3.4.3 (R Development Team, Vienna, Austria).

Results

Patient characteristics

The characteristics of the patients in the LR and IMRT

Table 1 The clinicopathological features of all patients in our study before PSM (n=307)

Variables	LR (n=140)	IMRT (n=167)	P
Age, year	52.0 (48.0–58.0)	53.0 (47.0–64.0)	0.186
Sex			0.069
Male	126 (90.0)	137 (82.0)	
Female	14 (10.0)	30 (18.0)	
HBsAg			0.896
No	16 (11.4)	21 (12.6)	
Yes	124 (88.6)	146 (87.4)	
Anti-viral treatment			0.759
No	122 (87.1)	146 (87.4)	
Yes	18 (12.9)	21 (12.5)	
Satellite nodules			0.053
No	105 (75.0)	107 (64.1)	
Yes	35 (25.0)	60 (35.9)	
Tumor capsulation			<0.001
No	8 (5.7)	28 (16.8)	
Incomplete	82 (58.6)	107 (64.1)	
Complete	50 (35.7)	32 (19.2)	
Lymph node invasion			0.273
No	128 (91.4)	145 (86.8)	
Yes	12 (8.6)	22 (13.2)	
Ascites			0.014
No	114 (81.4)	153 (91.6)	
Yes	26 (18.6)	14 (8.4)	
No. of tumor			0.005
Single	114 (81.4)	111 (66.5)	
Multiple	26 (18.6)	56 (33.5)	
AFP, ng/mL			0.950
<400	66 (47.1)	81 (48.5)	
400–1,000	13 (9.3)	14 (8.4)	
≥1,000	61 (43.6)	72 (43.1)	
Child-Pugh grade	140 (45.6)	167 (54.4)	0.063
A	137 (97.9)	156 (93.4)	
B	3 (2.1)	11 (6.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	LR (n=140)	IMRT (n=167)	P
Tumor diameter, cm	8 (4.8–10.8)	10.3 (8.0–12.9)	<0.001
PT, s	12.5 (11.6–13.4)	12.4 (11.7–12.9)	0.141
ALT, U/L	37.7 (25.0–63.5)	40.0 (24.6–70.0)	0.460
TP, g/L	67.75 (62.4–71.8)	67.7 (63.9–71.6)	0.844
ALB, g/L	39.6 (36.7–43.15)	38.4 (34.8–41.5)	0.009
AST, U/L	44.0 (31.0–65.0)	52.0 (36.0–81.0)	0.005
GGT, U/L	117.5 (53.5–203.0)	140.0 (75.0–237.0)	0.046
ALP, U/L	107.0 (85.0–143.0)	104.0 (88.0–152.0)	0.748
PLT, 10^9/L	159.0 (86.0–203.0)	158.0 (109.0–205.0)	0.665
TBIL, μmol/L	15.8 (13.2–20.6)	15.8 (11.8–20.5)	0.343
DBIL, μmol/L	8.8 (6.7–12.5)	9.3 (6.3–12.5)	0.778
Extent of HVTT			0.319
pHVTT	42 (30.0)	54 (32.3)	
mHVTT	54 (38.6)	51 (30.5)	
IVCTT	44 (31.4)	62 (37.1)	
Extent of PVTT			0.021
No	89 (63.6)	80 (47.9)	
Type I	30 (21.4)	48 (28.7)	
Type II	21 (15.0)	39 (23.4)	

Data are the median (IQR) or number (percentage) unless otherwise indicated. PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; LR, liver resection; HBsAg, hepatitis B surface antigen; AFP, α -fetoprotein; PT, prothrombin time; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; HVTT, hepatic vein tumor thrombus; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus.

groups before PSM are shown in *Table 1*. Patients in the IMRT group had higher rates of absence of ascites, multiple tumors, large tumor diameter, high levels of AST and GGT, and presence of PVTT than the patients in the LR group (all P<0.05). After PS matching, all these clinicopathological features became well-balanced between the two groups (*Table 2*).

Univariate and multivariate analyses of predictors of OS and RFS

Before PSM, uni- and multi-variate analyses demonstrated that presence of ascites (P=0.029), tumor diameter (P=0.005), extent of HVTT (P<0.001), extent of PVTT (P=0.001), and treatment modality (P<0.001) were independently related to OS (*Table 3*), whereas tumor diameter (P=0.021), level of AST (P=0.026), extent of HVTT (P<0.001), extent of PVTT (P=0.001), and treatment modality (P<0.001) were independently related to RFS (Table S1).

After PSM, uni- and multi-variate analyses demonstrated that extent of HVTT (P<0.001), and treatment modality (P<0.001) were independently related to OS (Table S2), whereas presence of ascites (P=0.029), extent of HVTT (P<0.001), and treatment modality (P<0.001) were independently related to RFS (Table S3).

Survival analysis before and after PSM

Before PSM, the median OS times (MOST 95% CI)

Table 2 The clinicopathological features of all patients in our study after PSM (n=164)

Variables	LR (n=82)	IMRT (n=82)	P
Age, year	52.0 (48.0–63.0)	53.5 (46.0–66.0)	0.875
Sex			1.000
Male	72 (87.8)	72 (87.8)	
Female	10 (12.2)	10 (12.2)	
HBsAg			1.000
No	10 (12.2)	11 (13.4)	
Yes	72 (87.8)	71 (86.6)	
Anti-viral treatment			0.815
No	71 (86.6)	72 (87.8)	
Yes	11 (13.4)	10 (12.2)	
Satellite nodules			0.303
No	55 (67.1)	61 (74.4)	
Yes	27 (32.9)	21 (25.6)	
Tumor capsulation			0.447
No	8 (9.8)	9 (11.0)	
Incomplete	61 (74.4)	54 (65.9)	
Complete	13 (15.9)	19 (23.2)	
Lymph node invasion			0.787
No	75 (91.5)	74 (90.2)	
Yes	7 (8.5)	8 (9.8)	
Ascites			0.393
No	67 (81.7)	71 (86.6)	
Yes	15 (18.3)	11 (13.4)	
No. of tumor			0.706
Single	63 (76.8)	65 (79.3)	
Multiple	19 (23.2)	17 (20.7)	
AFP, ng/mL			0.933
<400	32 (39.0)	34 (41.5)	
400–1,000	8 (9.8)	7 (8.5)	
≥1,000	42 (51.2)	41 (50.0)	
Child-Pugh grade			1.000
A	79 (96.3)	80 (97.6)	
B	3 (3.7)	2 (2.4)	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	LR (n=82)	IMRT (n=82)	P
Tumor diameter, cm	10.0 (6.0–12.0)	9.9 (7.1–12.0)	0.260
PT, s	12.5 (11.4–13.4)	12.6 (12.0–13.0)	0.841
ALT, U/L	36.2 (19.0–51.0)	39.4 (24.0–76.0)	0.223
TP, g/L	67.1 (63.5–70.5)	68.0 (64.1–71.7)	0.382
ALB, g/L	38.7 (35.3–42.0)	40.3 (37.4–42.2)	0.278
AST, U/L	40.0 (31.0–59.0)	48.5 (37.0–69.0)	0.036
GGT, U/L	86.0 (49.0–215.0)	136.0 (75.0–214.0)	0.185
ALP, U/L	107.0 (90.0–145.0)	97.0 (84.0–138.0)	0.292
PLT, 10^9/L	158.5 (85.0–216.0)	152.0 (108.0–188.0)	0.569
TBIL, μmol/L	15.9 (13.6–22.2)	15.2 (11.4–18.9)	0.054
DBIL, μmol/L	8.8 (6.8–12.7)	9.2 (6.6–11.9)	0.835
Extent of HVTT			0.220
pHVTT	18 (22.0)	28 (34.1)	
mHVTT	29 (35.4)	24 (29.3)	
IVCTT	35 (42.7)	30 (36.6)	
Extent of PVTT			0.328
No	49 (59.8)	45 (54.9)	
Type I	20 (24.4)	28 (34.1)	
Type II	13 (15.9)	9 (11.0)	

Data are the median (IQR) or number (percentage) unless otherwise indicated. PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; LR, liver resection; HBsAg, hepatitis B surface antigen; AFP, α -fetoprotein; PT, prothrombin time; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; HVTT, hepatic vein tumor thrombus; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus.

of the LR and IMRT groups were 21.0 (17.0–25.9) and 16.5 (14.6–18.5) months, respectively. The LR group had significantly higher OS rates than the IMRT group (1-year, 67.5% *vs.* 66.8%; 2-year, 45.0% *vs.* 29.9%; 3-year, 20.7% *vs.* 10.6%; 5-year, 7.8% *vs.* 1.0%; P=0.004, *Figure 2A*). The median RFS times (MRFST 95% CI) of the LR and IMRT groups were 13.0 (10.0–15.5) and 9.7 (6.6–12.5) months, respectively. The LR group had significantly better RFS rates than the IMRT group (1-year, 51.8% *vs.* 43.7%; 2-year, 21.5% *vs.* 13.9%; 3-year, 7.5% *vs.* 1.4%; 5-year, 2.5% *vs.* 0%; P=0.004, *Figure 2B*).

After PSM, the MOST (95% CI) of the two groups were 22.0 (17.5–25.9) and 16.8 (14.0–21.0) months, respectively. The OS rates were significantly better in the LR group than the IMRT group (1-year, 70.4% *vs.* 67.7%; 2-year, 44.5% *vs.* 29.4%; 3-year, 17.6% *vs.* 9.4%; 5-year, 6.5% *vs.* 0%; P=0.018, *Figure 2C*). The MRFST (95% CI) of the two groups were 14.5 (10.0–17.0) and 10.0 (6.3–13.4) months, respectively. The RFS rates were significantly better in the LR group than the IMRT group (1-year, 55.4% *vs.* 45.8%; 2-year, 21.4% *vs.* 14.0%; 3-year, 6.1% *vs.* 1.4%; 5-year, 1.5% *vs.* 0%; P=0.034, *Figure 2D*).

Subgroup analysis on the survival of patients with HVTT (pHVTT and mHVTT), IVCTT, and PVTT

For HCC patients with HVTT (pHVTT and mHVTT), the OS rates were significantly higher in the LR group than the IMRT group before PSM (1-year, 79.2% *vs.* 63.8%; 2-year, 55.2% *vs.* 35.2%; 3-year, 23.7% *vs.* 14.6%;

Table 3 Univariate and multivariable analysis for OS in HCC patients with HVTT before PSM (n=307)

Variables	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age, year	0.000	1.000 (0.989–1.011)	0.982			
Sex, female *vs.* male	–0.010	0.985 (0.709–1.367)	0.928			
HBsAg, yes *vs.* no	0.044	1.045 (0.730–1.496)	0.809			
Anti-viral treatment, yes *vs.* no	0.039	1.040 (0.724–1.490)	0.831			
Satellite nodules, yes *vs.* no	0.099	1.104 (0.859–1.418)	0.438			
Tumor capsulation						
Incomplete *vs.* no	0.322	1.380 (0.930–2.041)	0.106			
Complete *vs.* no	0.195	1.216 (0.797–1.850)	0.363			
Lymph node invasion, yes *vs.* no	–0.050	0.947 (0.648–1.384)	0.779			
Ascites, yes *vs.* no	0.39	1.489 (1.061–2.090)	0.021	0.382	1.465 (1.040–2.063)	0.029
Multiple tumor, yes *vs.* no	–0.070	0.923 (0.708–1.204)	0.557			
AFP, ng/mL						
400–1,000 *vs.* <400	0.219	1.245 (0.797–1.944)	0.335			
≥1,000 *vs.* <400	0.242	1.273 (0.997–1.627)	0.053			
Child-Pugh grade, A *vs.* B	0.357	1.430 (0.800–2.550)	0.227			
Tumor diameter, cm	0.041	1.041 (1.009–1.075)	0.010	0.048	1.048 (1.014–1.080)	0.005
PT, s	0.025	1.026 (0.948–1.110)	0.517			
ALT, U/L	0.000	0.998 (0.997–0.999)	0.043			
TP, g/L	0.005	1.005 (0.987–1.020)	0.534			
ALB, g/L	0.001	1.001 (0.900–1.027)	0.922			
AST, U/L	0.000	0.997 (0.995–0.999)	0.026			
GGT, U/L	0.000	0.999 (0.998–1.000)	0.576			
ALP, U/L	0.000	0.999 (0.998–1.001)	0.708			
PLT, 10^9/L	0.001	1.001 (0.999–1.002)	0.192			
TBIL, μmol/L	0.000	0.996 (0.991–1.001)	0.178			
DBIL, μmol/L	–0.010	0.982 (0.963–1.003)	0.095			
Extent of HVTT						
mHCTT *vs.* pHVTT	0.119	1.127 (0.844–1.504)	0.416	0.118	1.125 (0.831–1.522)	0.444
IVCTT *vs.* pHVTT	0.802	2.231 (1.668–2.900)	0.267	0.860	2.360 (1.746–3.197)	<0.001
Extent of PVTT						
Type I *vs.* no	0.340	1.405 (1.057–1.866)	0.018	0.437	1.547 (1.147–2.087)	0.004
Type II *vs.* no	0.498	1.646 (1.202–2.255)	0.001	0.548	1.730 (1.243–2.409)	0.001
Treatment, LR *vs.* IMRT	–0.290	0.741 (0.586–0.936)	0.012	–0.648	0.523 (0.403–0.600)	<0.001

OS, overall survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; LR, liver resection; HBsAg, hepatitis B surface antigen; AFP, α -fetoprotein; PT, prothrombin time; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus.

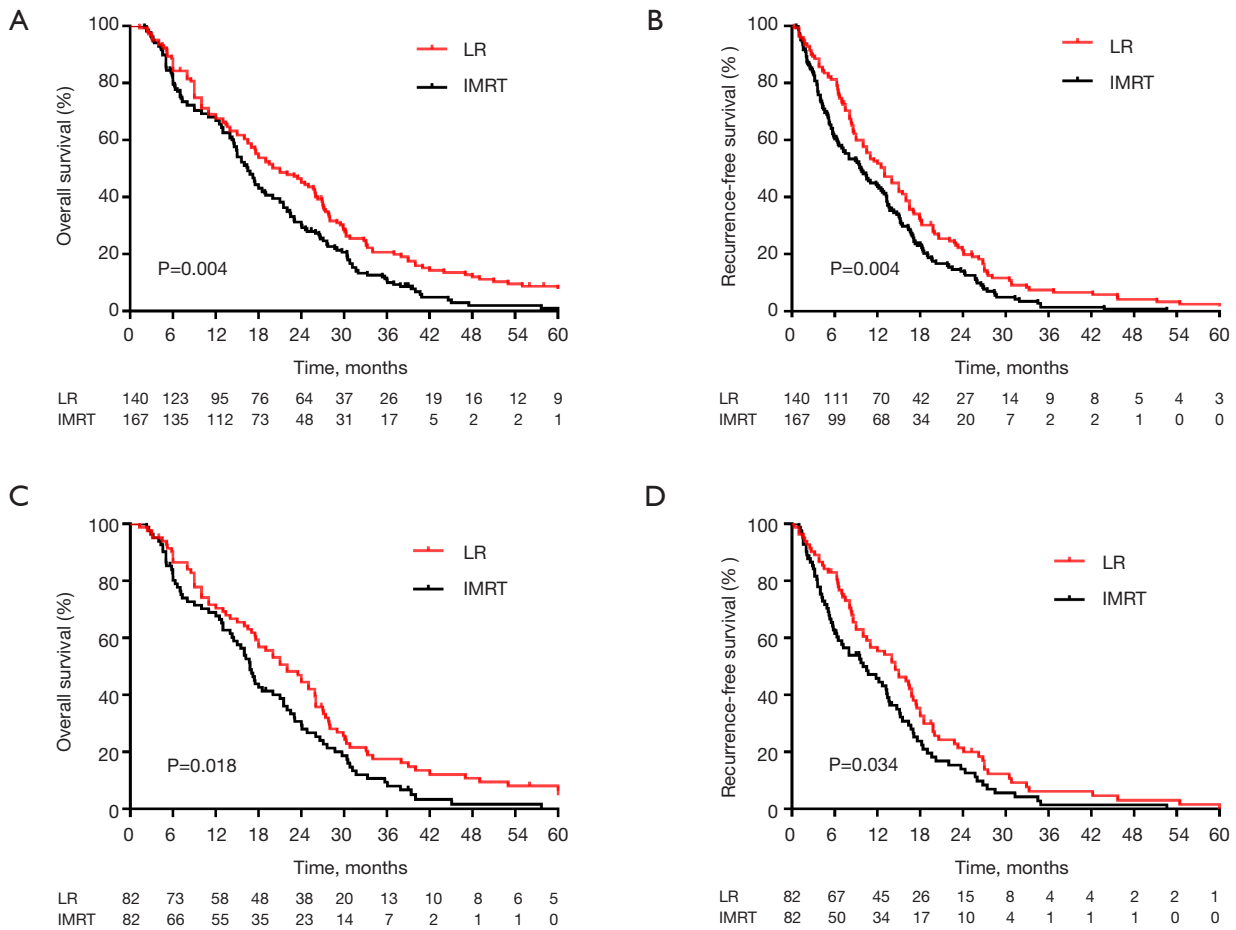

Figure 2 Kaplan-Meier analysis of OS and RFS in all HCC patients with HVTT. (A) The OS for HCC patients after LR or IMRT (140 *vs.* 167 patients) before PSM (P=0.004); (B) the RFS for HCC patients after LR or IMRT (140 *vs.* 167 patients) before PSM (P=0.004); (C) the OS for HCC patients after LR or IMRT (82 *vs.* 82 patients) after PSM (P=0.018); (D) the RFS for HCC patients after LR or IMRT (82 *vs.* 82 patients) after PSM (P=0.034). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; IMRT, intensity-modulated radiation therapy; LR, liver resection; PSM, propensity score matching.

5-year, 7.1% *vs.* 0%; P=0.002, *Figure 3A*). The RFS rates in the LR group were significantly higher than the IMRT group before PSM (1-year, 62.2% *vs.* 45.4%; 2-year, 28.9% *vs.* 16.5%; 3-year, 10.5% *vs.* 2.5%; 5-year, 3.5% *vs.* 0%; P=0.003, *Figure 3B*). After PSM, the OS and RFS rates were also significantly higher in the LR group than the IMRT group (OS: 1-year, 82.2% *vs.* 62.2%; 2-year, 55.6% *vs.* 28.9%; 3-year, 24.9% *vs.* 11.0%; 5-year, 3.3% *vs.* 0%; P=0.014, *Figure 3C*; RFS: 1-year, 64.4% *vs.* 46.4%; 2-year, 28.7% *vs.* 15.3%; 3-year, 10.5% *vs.* 3.1%; 5-year, 2.6% *vs.* 0%; P=0.037, *Figure 3D*). For HCC patients with pHVTT and mHVTT, LR had better OS and RFS rates than IMRT as shown in Figure S1 (P=0.018 and P=0.027).

For HCC patients with IVCTT, there were no significant differences in the OS and RFS rates between the two groups of patients before PSM (OS: P=0.986, *Figure 4A*; RFS: P=0.557, *Figure 4B*). After PSM, there were also no significant difference in OS and RFS rates for the two groups of patients (OS: P=0.821, *Figure 4C*; RFS: P=0.657, *Figure 4D*).

For patients who underwent LR, the median OS and RFS were significantly higher in patients without PVTT than those with PVTT (P<0.001, Figure S2). Similarly, for patients who underwent IMRT, the no-PVTT subgroup had higher median OS and RFS than the PVTT group (P<0.001, Figure S2).

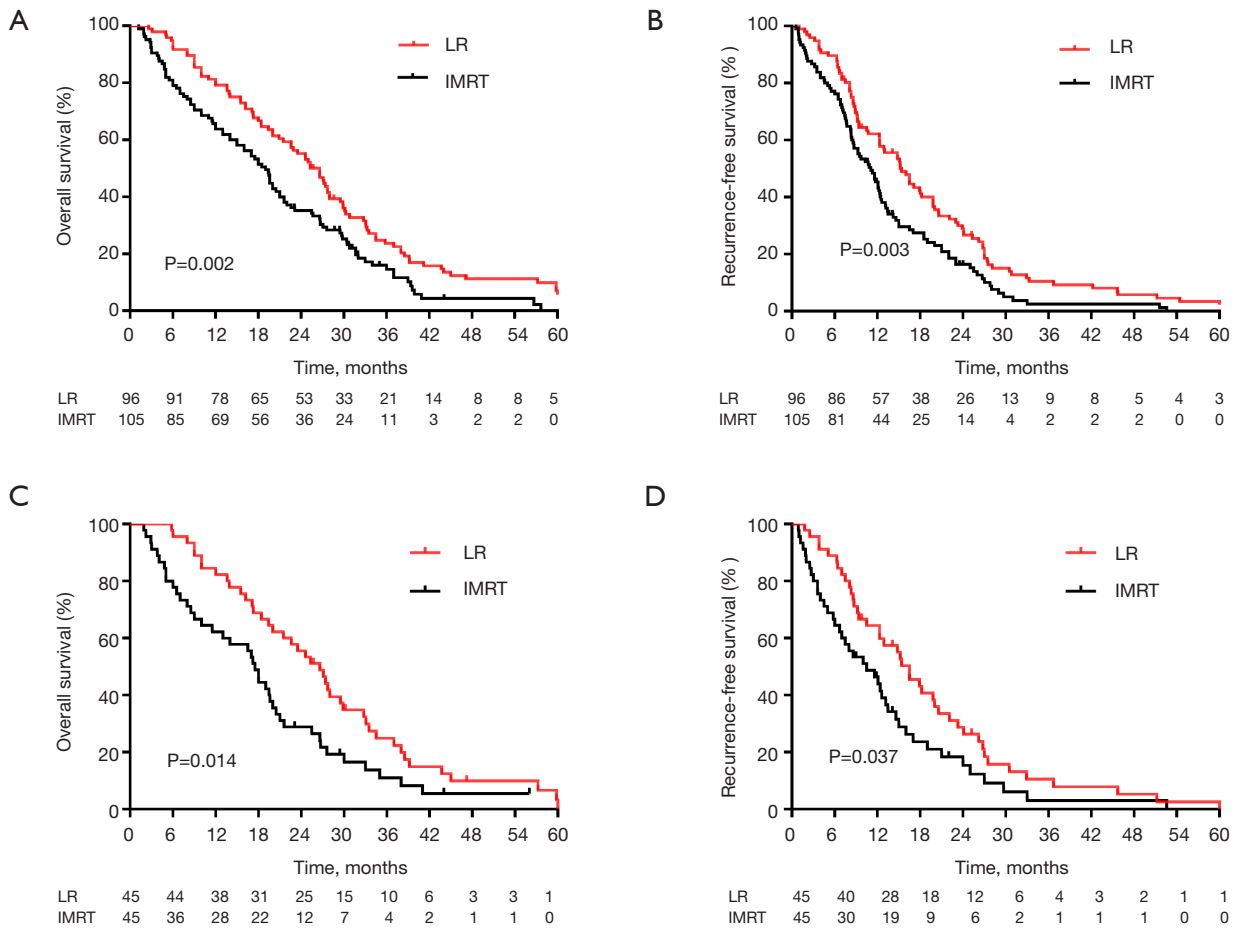

Figure 3 Kaplan-Meier subgroup analysis of OS and RFS in HCC patients with HVTT (pHVTT and mHVTT). (A) The OS for HCC patients after LR or IMRT (96 *vs.* 105 patients) before PSM (P=0.002); (B) the RFS for HCC patients after LR or IMRT (96 *vs.* 105 patients) before PSM (P=0.003); (C) the OS for HCC patients after LR or IMRT (45 *vs.* 45 patients) after PSM (P=0.014); (D) the RFS for HCC patients after LR or IMRT (45 *vs.* 45 patients) after PSM (P=0.037). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IMRT, intensity-modulated radiation therapy; LR, liver resection; PSM, propensity score matching.

Adverse events of IMRT

Table S4 summarizes the toxicities of the CTCAE Grade 3–5 for all the patients who underwent IMRT. Fatigue, anorexia, and nausea were the most common acute toxicities, but most of them were in the CTCAE Grade 1 or 2. For gastrointestinal complications, 6 patients (3.6%) developed CTCAE Grade 3 mucositis or ulcers within the radiation field. No treatment-related deaths or serious adverse events were observed in this study.

Detailed procedures and outcomes of LR

As shown in Table S5, there were 115 (82.1%) patients undergoing R0 resection, 89 (63.6%) patients major hepatectomy, and 86 (61.4%) anatomical resection. The median hospital stay was 19 [14–24] days. Morbidity and mortality were described according to the Clavien-Dindo classification. The majority of complications of LR belonged to Clavien-Dindo grade I (15.7%) or grade II (12.9%). A total of seven patients (5.0%) experienced grade III complications due to pulmonary infection (n=2) and pulmonary embolism (n=5). Two patients (1.4%) experienced severe liver failure and received comprehensive treatment in intensive. No one died from complications of LR during the study period. There were only 5 patients experienced pulmonary embolism in the surgery group.

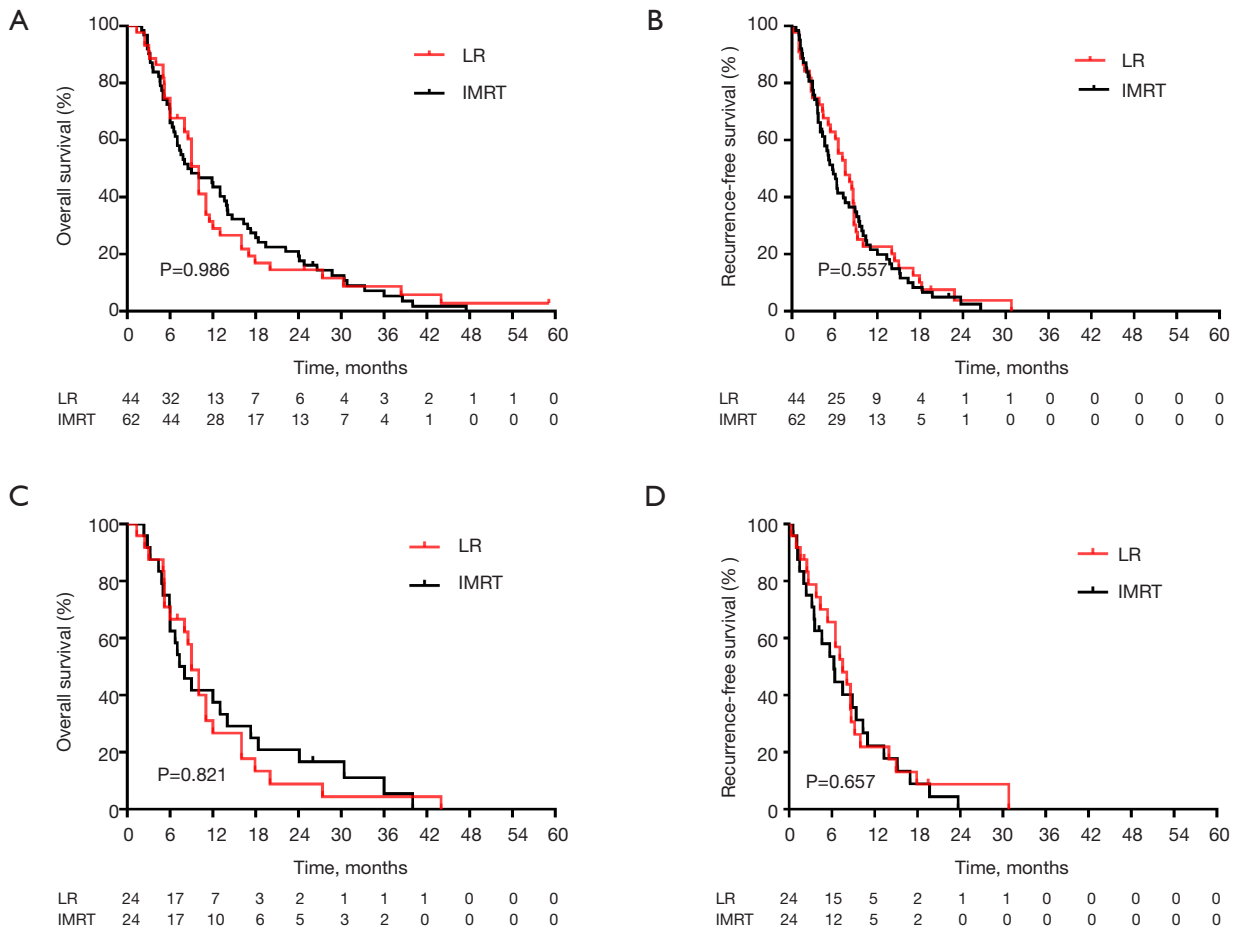

Figure 4 Kaplan-Meier subgroup analysis of OS and RFS in HCC patients with IVCTT. (A) The OS for HCC patients after LR or IMRT (44 *vs.* 62 patients) before PSM (P=0.986); (B) the RFS for HCC patients after LR or IMRT (44 *vs.* 62 patients) before PSM (P=0.557); (C) the OS for HCC patients after LR or RT (24 *vs.* 24 patients) after PSM (P=0.821); (D) the RFS for HCC patients after LR or IMRT (24 vs. 24 patients) after PSM (4D) (P=0.657). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; IVCTT, inferior vena cava tumor thrombus; IMRT, intensity-modulated radiation therapy; LR, liver resection; PSM, propensity score matching.

Discussion

Macrovascular invasion has been well recognized as one of the most important poor prognostic factors of long-term survival in HCC patients (24,25). The prognosis for HCC patients with HVTT is extremely poor (3,26). Paucity of data on management of HCC patients with HVTT has made treatment decisions difficult, and the optimal choice of treatment for this subgroup of patients remains controversial. Recently, a Japanese nationwide survey demonstrated that LR produced reasonably good prognosis in selected HCC patients with HVTT, especially in those without PVTT (9). This large sample size study showed superiority of LR over non-LR treatments.

Recent developments in radiation techniques have enabled safe delivery of dose-escalated conformal radiotherapy to a wide spectrum of patients with inoperable HCC and liver metastases (27,28). Promising clinical data on radiotherapy for unresectable HCC suggested that HCC is radiosensitive, with sustained local control rates ranging from 71% to 100% (29,30). Recently, RT was shown to be effective in treating unresectable HCC with PVTT. Lin *et al.* reported that stereotactic or three-dimensional conformal RT (3D-CRT) could result in recanalization of PVTT in unresectable HCC and that the responders showed significantly better 1- and 2-year OS rates than non-responders (31).

The optimal treatment for HCC patients with HVTT

remains highly debatable. Our study demonstrated that patients with HVTT undergoing LR had significantly better long-term OS than those undergoing IMRT, indicating that in selected patients LR was the better treatment for these patients. Moreover, Nakano *et al.* demonstrated that surgery provided better long-term OS and disease-free survival in patients with small HCC tumors (32). On subgroup analysis, LR was a better treatment than IMRT for HCC patients with pHVTT and nHVTT, but not for patients with IVCTT. In our study, 138 of 307 HVTT patients (45%) also had PVTT. The coexistent rate of PVTT and HVTT in our study was higher than those reported by others (3,18,29).

This coexistence had a poorer prognosis than HVTT alone. Recent studies showed epithelial-mesenchymal transition (EMT), the mechanism involved in invasion in a variety of cancers (33), to be involved in vascular invasion in HCC. This may explain why there was a high coexistent rate of PVTT and HVTT in our study. This high coexistent rate was also found to be a significant risk factor of OS and RFS on univariate and multivariate analyses before and after PSM. However, why PVTT more commonly occurs than HVTT is unclear and requires further research.

For patients with IVCTT, available medical evidence to guide treatment is scarce, probably because of its rarity and the technical difficulty in its treatment. Wang *et al.* conducted a retrospective study on 56 IVCTT patients and showed significantly better MST in the 25 patients treated with surgery (34). Another Japanese study with a large sample size which involved 245 IVCTT patients demonstrated survival benefit of surgical over nonsurgical treatment (9). These two studies demonstrated surgery, although technically challenging, could safely be performed in IVCTT patients and resulted in better long-term survival outcomes than non-surgical treatment. In our study, LR and IMRT resulted in similar long-term survival in IVCTT patients. Such a result is probably because of the better local control capacity on IVCTT by the improved technology of irradiation using IMRT. A study from Japan also demonstrated beneficial effects of another improved radiation technology of 3D-CRT on HCC with IVCTT (35,36). A novel RT technology, particle radiotherapy, has emerged to be a potential treatment for HCC patients with stage IIIB IVCTT and stage IV disease (37,38).

This study had several limitations. First, the etiology of HCC in this large series coming from China is mainly hepatitis B virus infection. Thus, the results of this study may not be applicable to HCC with other etiologies. Second, it was difficult to select HCC patients with only HVTT without coexisting PVTT due to the high incidence of PVTT and the low incidence of HVTT. Thus, there is a high percentage of patients with coexistence of HVTT and PVTT in our study. Third, this is a retrospective study with its inherent defects.

In conclusion, LR was associated with better survival outcomes in HCC patients with hepatic vein tumor thrombus (pHVTT and mHVTT) than IMRT. However, for HCC patients with IVCTT, LR showed no survival benefit compared to IMRT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.20/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.20/coif). The authors have no conflicts of interest to declare. Dr. WYL serves as the unpaid editorial board members of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the Eastern Hepatobiliary Surgery Hospital (Permit Number: HBHKY-2019-001-017). Informed consent was obtained from all the patients prior

to treatment.

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Supplementary

Table S1 Univariate and multivariable analysis for RFS in HCC patients with HVTT before PSM (n=307)

Clinical variables	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age, year	0.000	1.000 (0.990–1.011)	0.915			
Sex, female *vs.* male	–0.180	0.835 (0.597–1.167)	0.292			
HBsAg, yes *vs.* no	0.064	1.066 (0.827–1.374)	0.617			
Anti-viral treatment, yes *vs.* no	–0.094	0.910 (0.558–1.480)	0.706			
Satellite nodules, yes *vs.* no	0.353	1.424 (0.976–2.077)	0.066			
Tumor capsulation						
Incomplete *vs.* no	0.266	1.305 (0.866–1.966)	0.203			
Complete *vs.* no	0.040	1.041 (0.720–1.506)	0.828			
Lymph node invasion, yes *vs.* no	0.156	1.169 (0.819–1.667)	0.387			
Ascites, yes *vs.* no	0.449	1.566 (1.110–2.210)	0.010			
Multiple tumor, yes *vs.* no	–0.050	0.940 (0.727–1.229)	0.675			
AFP, ng/mL						
400–1,000 *vs.* <400	0.104	1.109 (0.711–1.732)	0.648			
≥1,000 *vs.* <400	0.222	1.248 (0.976–1.596)	0.077			
Child-Pugh grade, A *vs.* B	0.401	1.493 (0.834–2.673)	0.176			
Tumor diameter, cm	0.030	1.030 (0.998–1.063)	0.019	0.038	1.039 (1.005–1.073)	0.021
PT, s	0.019	1.019 (0.949–1.095)	0.590			
ALT, U/L	0.000	0.998 (0.996–0.999)	0.022			
TP, g/L	0.000	0.990 (0.977–1.010)	0.692			
ALB, g/L	0.000	0.993 (0.968–1.019)	0.641			
AST, U/L	0.000	0.996 (0.994–0.990)	0.007	–0.003	0.997 (0.994–0.999)	0.026
GGT, U/L	0.000	0.999 (0.998–1.000)	0.261			
ALP, U/L	0.000	0.900 (0.998–1.001)	0.578			
PLT, 10^9/L	0.000	1.000 (0.999–1.002)	0.278			
TBIL, μmol/L	0.000	0.996 (0.991–1.001)	0.131			
DBIL, μmol/L	–0.010	0.980 (0.962–1.001)	0.070			
Extent of HVTT						
mHCTT *vs.* pHVTT	0.325	1.385 (1.037–1.849)	0.027	0.287	1.332 (0.980–1.810)	0.066
IVCTT *vs.* pHVTT	1.014	2.757 (2.037–3.733)	<0.001	1.127	3.080 (2.252–4.200)	<0.001
Extent of PVTT						
Type I *vs.* no	0.305	1.357 (1.023–1.79)	0.033	0.487	1.627 (1.209–2.189)	0.001
Type II *vs.* no	0.278	1.321 (0.961–1.814)	0.085	0.307	1.359 (0.976–1.894)	0.069
Treatment, LR *vs.* IMRT	–0.400	0.665 (0.526–0.841)	<0.001	–0.727	0.483 (0.370–0.623)	<0.001

RFS, recurrence-free survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; LR, liver resection; HBsAg, hepatitis B surface antigen; AFP, α -fetoprotein; PT, prothrombin time; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus.

https://dx.doi.org/10.21037/hbsn.2020.03.20

Table S2 Univariate and multivariable analysis for OS in HCC patients with HVTT after PSM (n=164)

Variables	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age, year	–0.006	0.994 (0.980–1.008)	0.441			
Sex, female *vs.* male	–0.052	0.949 (0.580–1.552)	0.836			
HBsAg, yes *vs.* no	–0.210	0.810 (0.577–1.136)	0.223			
Anti-viral treatment, yes *vs.* no	0.211	1.234 (0.859–1.773)	0.254			
Satellite nodules, yes *vs.* no	–0.015	0.980 (0.570–1.700)	0.958			
Tumor capsulation						
Incomplete *vs.* no	–0.052	0.948 (0.517–1.741)	0.866			
Complete *vs.* no	–0.180	0.835 (0.489–1.424)	0.509			
Lymph node invasion, yes *vs.* no	–0.005	0.994 (0.615–1.608)	0.983			
Ascites, yes *vs.* no	0.461	1.586 (1.050–2.395)	0.028			
Multiple tumor, yes *vs.* no	–0.106	0.899 (0.620–1.302)	0.574			
AFP, ng/mL						
400–1,000 *vs.* <400	0.009	1.009 (0.553–1.842)	0.976			
≥1,000 *vs.* <400	–0.009	0.991 (0.712–1.380)	0.959			
Child-Pugh grade, A *vs.* B	1.162	3.000 (0.995–10.25)	0.051			
Tumor diameter, cm	0.005	1.000 (0.961–1.050)	0.819			
PT, s	–0.003	0.997 (0.875–1.136)	0.966			
ALT, U/L	0.000	0.999 (0.996–1.002)	0.766			
TP, g/L	–0.003	0.996 (0.970–1.020)	0.810			
ALB, g/L	0.006	1.005 (0.968–1.043)	0.772			
AST, U/L	–0.003	0.996 (0.992–1.000)	0.126			
GGT, U/L	–0.001	0.999 (0.998–1.000)	0.273			
ALP, U/L	0.000	0.999 (0.997–1.001)	0.629			
PLT, 10^9/L	0.000	1.000 (0.998–1.002)	0.929			
TBIL, μmol/L	0.003	1.002 (0.997–1.008)	0.319			
DBIL, μmol/L	0.008	1.007 (0.975–1.040)	0.637			
Extent of HVTT						
mHCTT *vs.* pHVTT	0.033	1.033 (0.693–1.542)	0.870	0.098	1.103 (0.735–1.653)	0.635
IVCTT *vs.* pHVTT	1.073	2.922 (1.959–4.358)	<0.001	1.407	4.080 (2.650–6.294)	<0.001
Extent of PVTT						
Type I *vs.* no	0.050	1.051 (0.728–1.517)	0.789			
Type II *vs.* no	0.392	1.480 (0.954–2.295)	0.080			
Treatment, LR *vs.* IMRT	–0.918	0.399 (0.288–0.551)	<0.001	–1.139	0.320 (0.227–0.450)	<0.001

OS, overall survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; LR, liver resection; HBsAg, hepatitis B surface antigen; AFP, α -fetoprotein; PT, prothrombin time; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus.

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Table S3 Univariate and multivariable analysis for RFS in HCC patients with HVTT after PSM (n=164)

Clinical variables	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age, year	0.000	0.993 (0.980–1.007)	0.380			
Sex, female *vs.* male	–0.100	0.901 (0.549–1.477)	0.680			
HBsAg, yes *vs.* no	–0.190	0.823 (0.586–1.156)	0.261			
Anti-viral treatment, yes *vs.* no	0.175	1.190 (0.731–1.937)	0.482			
Satellite nodules, yes *vs.* no	0.035	1.035 (0.598–1.791)	0.900			
Tumor capsulation						
Incomplete *vs.* no	0.009	1.009 (0.544–1.871)	0.975			
Complete *vs.* no	–0.090	0.900 (0.529–1.547)	0.715			
Lymph node invasion, yes *vs.* no	0.080	1.091 (0.673–1.768)	0.721			
Ascites, yes *vs.* no	0.587	1.800 (1.180–2.744)	0.000	0.478	1.613 (1.049–2.480)	0.029
Multiple tumor, yes *vs.* no	–0.060	0.939 (0.648–1.359)	0.739			
AFP, ng/mL						
400–1,000 *vs.* <400	0.055	1.057 (0.598–1.866)	0.850			
≥1,000 *vs.* <400	–0.092	1.096 (0.784–1.532)	0.591			
Child-Pugh grade, A *vs.* B	0.810	2.255 (0.709–7.172)	0.168			
Tumor diameter, cm	0.000	1.009 (0.966–1.054)	0.669			
PT, s	0.000	0.974 (0.850–1.112)	0.703			
ALT, U/L	0.000	0.998 (0.990–1.001)	0.431			
TP, g/L	0.000	0.993 (0.967–1.019)	0.627			
ALB, g/L	0.011	1.011 (0.976–1.047)	0.530			
AST, U/L	0.000	0.996 (0.991–1.000)	0.074			
GGT, U/L	0.000	0.999 (0.998–1.00)	0.101			
ALP, U/L	0.000	0.999 (0.997–1.001)	0.656			
PLT, 10^9/L	0.000	1.000 (0.998–1.002)	0.800			
TBIL, μmol/L	0.000	1.000 (0.990–1.010)	0.929			
DBIL, μmol/L	0.000	1.000 (0.966–1.035)	0.981			
Extent of HVTT						
mHCTT *vs.* pHVTT	0.270	1.310 (0.883–1.944)	0.178	0.371	1.449 (0.969–2.160)	0.070
IVCTT *vs.* pHVTT	1.083	2.950 (1.940–4.501)	<0.001	1.269	3.558 (2.283–5.545)	<0.001
Extent of PVTT						
Type I *vs.* no	–0.010	0.988 (0.689–1.418)	0.951			
Type II *vs.* no	0.135	1.145 (0.735–1.784)	0.548			
Treatment, LR *vs.* IMRT	–0.930	0.391 (0.282–0.541)	<0.001	–1.119	0.326 (0.230–0.458)	<0.001

RFS, recurrence-free survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; LR, liver resection; HBsAg, hepatitis B surface antigen; AFP, α -fetoprotein; PT, prothrombin time; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus.

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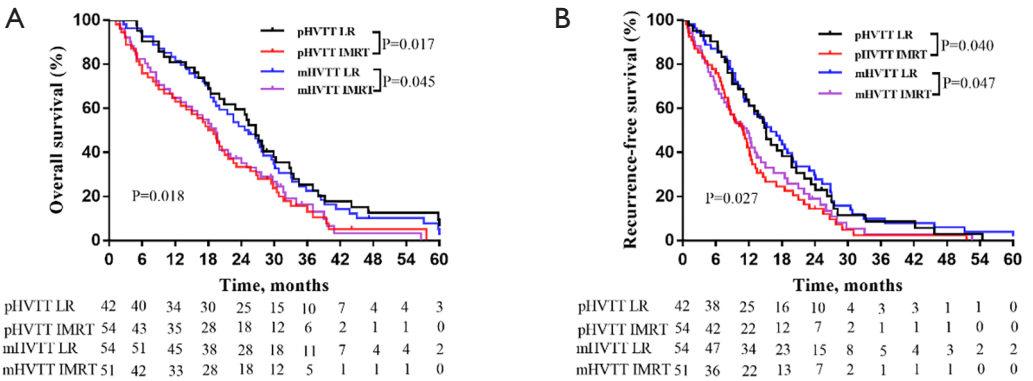

Figure S1 Kaplan-Meier analysis of OS and RFS of HCC patients with pHVTT and mHVTT of HVTT on subgroup analysis. (A) The OS for HCC patients after LR or IMRT (42 *vs.* 54 patients in pHVTT; 54 *vs.* 51 patients in mHVTT) after LR (P=0.018); (B) the RFS for HCC patients after LR or IMRT (42 *vs.* 54 patients in pHVTT; 54 *vs.* 51 patients in mHVTT) after LR (P=0.027). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; pHVTT, peripheral type of HVTT; mHVTT, major type of HVTT; IMRT, intensity-modulated radiation therapy; LR, liver resection.

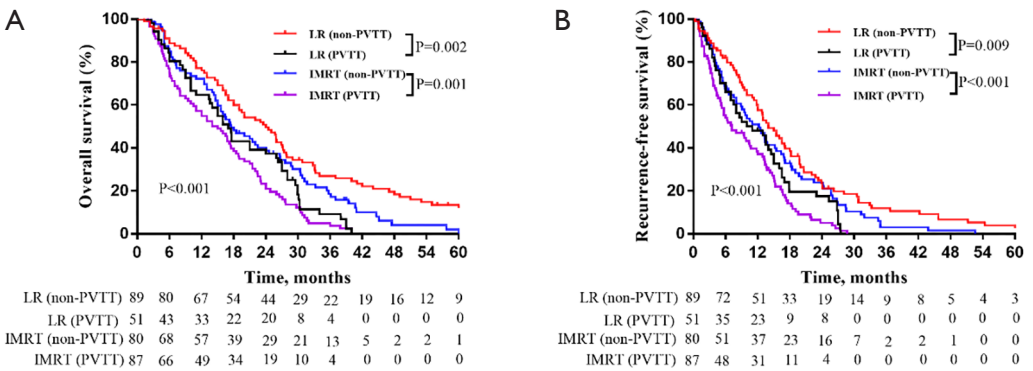

Figure S2 Kaplan-Meier analysis of OS and RFS in HCC patients with or without PVTT on subgroup analysis. (A) The OS for HCC patients with or without PVTT (87 *vs.* 80 patients after IMRT; 51 *vs.* 89 patients after LR) after LR (P<0.001); (B) the RFS for HCC patients with or without PVTT (87 *vs.* 80 patients after IMRT; 51 *vs.* 89 patients after LR) after LR (P<0.001). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; IMRT, intensity-modulated radiation therapy; LR, liver resection.

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Table S4 Adverse events of patients with HCC and HVTT who underwent IMRT

Adverse event	No. of patients with CTCAE grade (n)		
	3	4	5
Fatigue	3	–	–
Anorexia	2	2	–
Nausea	2	2	–
ALT increase	1	–	–
Bilirubin increase	1	1	–
Gastroduodenitis	1	–	–
Gastric ulcer	2	–	–
Duodenal ulcer	3	1	–

Adverse event was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; IMRT, intensity-modulated radiation therapy; ALT, alanine aminotransferase.

Table S5 Operative procedures and outcomes

Operative details	No. (%)
Major hepatectomy	89 (63.6)
Extent of resection	
R0	115 (82.1)
R1	25 (17.9)
Anatomical resection	86 (61.4)
Median hospital stay (days)	19 [14–24]
Clavien-dindo grade (total)	45 (32.1)
I	22 (15.7)
II	18 (12.9)
III	3 (2.1)
IV	2 (1.4)
V	0

Data are the median [IQR] or number (percentage) unless otherwise indicated.

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