Methods

Classification of Portal Vein Tumor Thrombosis:

Portal vein tumor thrombosis was classified as follows: Vp0, absence of invasion of (or tumor thrombus in) the portal vein; Vp1, invasion of (or tumor thrombus in) distal to the second order branches of the portal vein, but not of the second order branches; Vp2, invasion of (or tumor thrombus in) second order branches of the portal vein; Vp3, invasion of (or tumor thrombus in) first order branches of the portal vein; Vp4, invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contra-lateral portal vein branch to the primarily involved lobe. (*19,20*)

Assessment of the medical costs for the treatments

The Health Insurance Review & Assessment Service (HIRA) national patients sample (NPS) data is representative of South Korean population, which includes approximately 3% of the total population.(*22,23*) From the HIRA-NPS data, the claims for treatments (i.e., resection, TARE, radiofrequency ablation, percutaneous ethanol injection, transplantation, transarterial chemoembolization, external-beam radiation therapy, and systemic cytotoxic chemotherapy) were extracted. Drug costs were usually estimated based on 1 cycle of therapy. Dosing of the agents was estimated per standard of care as follows: sorafenib, 400 mg orally twice daily; lenvatinib, 8–12 mg once daily; regorafenib, 120 mg orally for 21 days of a 28-day treatment cycle; nivolumab, a 180 mg fixed dose intravenously every 2 weeks; cabozantinib 60 mg orally once daily; and pembrolizumab, a 200 mg fixed dose intravenously every 3 weeks.(*24*) The cost of systemic therapy was calculated by combining drug costs, dose estimated as mentioned above, and the treatment duration of each patient. The cost of clinical trials was excluded from this analysis.

Development of the propensity score model for inverse probability of treatment weighting:

Propensity scores of the initial treatment modality (transarterial radioembolization [TARE] or resection) were calculated by fitting a logistic regression model including all baseline characteristics variables (age, sex, etiology of hepatocellular carcinoma [HCC], presence of liver cirrhosis, albumin-bilirubin grade, alpha-fetoprotein level, presence of tiny satellite nodules, tumor size, extent of lobar involvement, and extent of portal vein tumor thrombosis [PVTT]). We performed weight truncation at the 1st and 99th percentiles to avoid the influence of extreme weights and used stabilized weights for inverse probability of treatment weighting (IPTW) analysis.(*28-30*) The balance of baseline characteristics between the two groups was reevaluated after IPTW.(*31*)

Supplemental Table 1. Imaging Studies: Modalities & Intervals

Whole patients	TARE (n=57)	Resection (n=500)	P value
Follow-up duration, months	19.0 (10.0–37.1)	41.2 (19.8–63.2)	<0.001
Number of overall liver imaging studies (per patients)	10.0 (6.0–15.0)	13.0 (7.0–19.0)	0.03
Interval between each imaging study, months (per patients)	2.0 (1.6–2.3)	3.0 (2.3–3.6)	<0.001
Number of each imaging modalities, N (%) (overall patients)			0.098
CT	490 (75.6%)	5419 (78.4%)	
MRI	158 (24.4%)	1491 (21.6%)	
Patients with tumor progression	**TARE (n=17)**	**Resection (n=244)**	**P value**
Interval between each imaging study, months (per patients)	1.9 (1.7–2.5)	2.5 (2.0–3.0)	0.004
The imaging interval at which the tumor progression was detected	2.8 (2.0–3.2)	2.9 (1.9–3.3)	0.75
Imaging tool that detected the tumor progression			0.87
CT	10 (58.8%)	123 (50.4%)	
MRI	7 (41.2%)	96 (39.3%)	
Non-liver imaging	0 (0.0%)	17 (7.0%)	
CT combined with non-liver imaging	0 (0.0%)	5 (2.0%)	
MRI combined with non-liver imaging	0 (0.0%)	3 (1.2%)	

Data are presented as N (%) or median (interquartile range).

CT, computed tomography; MRI, magnetic resonance imaging.

Supplemental Table 2. Risk Factor Analysis for Time to Progression

Variable	Univariable Analysis		Multivariable Analysis	
	Hazard ratio 95% CI	p-value	Hazard ratio 95% CI	p-value
Age ≥ 60 (vs. <60)	0.75 (0.45–1.22)	0.25		
Male (vs. female)	1.22 (0.72–2.07)	0.47		
ASA classification 3 (vs. 1 or 2)	1.59 (0.99–2.53)	0.053	0.79 (0.41–1.50)	0.47
HBV-related	1.12 (0.66–1.87)	0.68		
Liver cirrhosis	1.75 (1.09–2.81)	0.02	1.87 (0.92–3.83)	0.08
ALBI grade ≥2 (vs. 1)	1.38 (0.73–2.59)	0.32		
AFP ≥400 ng/mL (vs. <400 ng/mL)	0.86 (0.52–1.42)	0.56		
Satellite nodules	1.50 (1.12–2.00)	0.007	1.40 (1.01–1.95)	0.04
Tumor size ≥8 cm	1.45 (0.89–2.37)	0.14		
Bilobar involvement	1.36 (0.88–2.08)	0.16		
Vp2 (vs. Vp0-1)	1.56 (1.06–2.29)	0.02	1.67 (1.16–2.41)	0.006
TARE (vs. resection)	1.10 (0.55–2.20)	0.80	0.98 (0.50–1.95)	0.96

With weighted population, using variables with p value under 0.1 at univariable analysis

HBV, hepatitis B virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; Vp2, invasion of (or tumor thrombus in) second order branches of the portal vein; Vp0, absence of invasion of (or tumor thrombus in) the portal vein; Vp1, invasion of (or tumor thrombus in) distal to the second order branches of the portal vein, but not of the second order branches; TARE, transarterial radioembolization.

Supplemental Table 3. Risk Factor Analysis for Time to Intrahepatic Progression

Variable	Univariable Analysis		Multivariable Analysis	
	Hazard ratio 95% CI	p-value	Hazard ratio 95% CI	p-value
Age ≥ 60 (vs. <60)	0.83 (0.48–1.41)	0.49		
Male (vs. female)	1.22 (0.69–2.14)	0.50		
ASA classification 3 (vs. 1 or 2)	1.62 (0.97–2.69)	0.06	0.87 (0.43–1.73)	0.68
HBV-related	1.07 (0.61–1.86)	0.82		
Liver cirrhosis	1.77 (1.06–2.98)	0.03	1.73 (0.80–3.75)	0.16
ALBI grade ≥2 (vs. 1)	1.50 (0.78–2.86)	0.22		
AFP ≥400 ng/mL (vs. <400 ng/mL)	0.82 (0.49–1.39)	0.47		
Satellite nodules	1.54 (1.17–2.04)	0.002	1.41 (0.99–1.99)	0.054
Tumor size ≥8 cm	1.24 (0.74–2.08)	0.42		
Bilobar involvement	1.33 (0.84–2.12)	0.23		
Vp2 (vs. Vp0-1)	1.58 (1.05–2.38)	0.03	1.72 (1.18–2.50)	0.005
TARE (vs. resection)	1.45 (0.72–2.93)	0.30	1.30 (0.65–2.58)	0.46

With weighted population, using variables with p value under 0.1 at univariable analysis

HBV, hepatitis B virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; Vp2, invasion of (or tumor thrombus in) second order branches of the portal vein; Vp0, absence of invasion of (or tumor thrombus in) the portal vein; Vp1, invasion of (or tumor thrombus in) distal to the second order branches of the portal vein, but not of the second order branches; TARE, transarterial radioembolization.

Supplemental Table 4. Summary of Additional Treatment Modalities

	TARE (n=57)	Resection (n=500)	P value
Additional treatment before tumor progression			
TARE, N (%)	2 (3.5%)	0 (0.0%)	0.010
TACE, times (N)			<0.001
1	11 (19.3%)	0 (0.0%)	
2	5 (8.8%)	0 (0.0%)	
3	1 (1.8%)	0 (0.0%)	
Hepatic resection, N (%)	9 (15.8%)	0 (0.0%)	<0.001
Liver transplantation, N (%)	1 (1.8%)	0 (0.0%)	0.10
Intrahepatic RT, N (%)	1 (1.8%)	0 (0.0%)	0.10
Systemic therapy, N (%)	1 (1.8%)	0 (0.0%)	0.10
Total number of additional treatment before tumor progression*, N (%)			<0.001
1	16 (28.1%)	0 (0.0%)	
2	8 (14.0%)	0 (0.0%)	
3	2 (3.5%)	0 (0.0%)	
Additional treatment after tumor progression			
TARE	4 (7.0%)	2 (0.4%)	<0.001
TACE, times (N)			0.74
1	7 (12.3%)	53 (10.6%)	
2–3	6 (10.6%)	48 (9.6%)	
4–6	1 (1.8%)	29 (5.8%)	
≥ 7	1 (1.8%)	14 (2.8%)	
RFA, times (N)			0.87
1	6 (10.5%)	57 (11.4%)	
2–3	1 (1.8%)	15 (3.0%)	
4–6	0 (0.0%)	3 (0.6%)	
PEI	0 (0.0%)	3 (0.6%)	>0.99

Hepatic resection, times (N)			0.65
1	0 (0.0%)	11 (2.2%)	
2	0 (0.0%)	1 (0.2%)	
Metastasectomy, times (N)			0.70
1	1 (1.8%)	19 (3.8%)	
2–4	1 (1.8%)	12 (2.4%)	
Liver transplantation	0 (0.0%)	9 (1.8%)	0.61
Intrahepatic RT, times (N)			0.13
1	2 (3.5%)	23 (4.6%)	
2	1 (1.8%)	0 (0.0%)	
Extrahepatic RT, times (N)			0.42
1–2	3 (5.3%)	38 (7.6%)	
≥ 3	0 (0.0%)	11 (2.2%)	
Systemic therapy	11 (19.3%)	86 (17.2%)	0.83
Number of additional treatment after tumor progression per patient[†], N (%)			0.28
1	12 (21.1%)	71 (14.2%)	
2–3	11 (19.3%)	79 (15.8%)	
≥ 4	5 (8.8%)	80 (16.0%)	

Data are presented as number (%) or median (interquartile range).

[*]Systemic therapy is counted as 0 or 1 only depending on the treatment status regardless of the number or type of systemic agents.

TARE, transarterial radioembolization; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; RT, radiotherapy

Supplemental Table 5. Safety Assessment of TARE group

Adverse event	Therasphere® (n=45)		SIR-Spheres® (n=12)		P value	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Overall incidence	18 (40.0%)	3 (6.7%)	7 (58.3%)	2 (16.7%)	0.42	0.28
Ascites	0	0	0	0	N/A	N/A
Fever	3 (6.7%)	0	0	0	1.00	N/A
Nausea	3 (6.7%)	0	4 (33.3%)	0	0.03	N/A
Vomiting	1 (2.2%)	0	4 (33.3%)	0	0.006	N/A
Abdominal pain	12 (26.7%)	2 (4.4%)	3 (25.0%)	1 (8.3%)	1.00	0.52
Biliary anastomotic leak	0	0	0	0	N/A	N/A
Wound complication	0	0	0	0	N/A	N/A
Dyspnea	0	0	0	0	N/A	N/A
GI hemorrhage	0	0	0	0	N/A	N/A
AST elevation	3 (6.7%)	1 (2.2%)	1 (8.3%)	0	1.00	1.00
ALT elevation	2 (4.4%)	0	1 (8.3%)	1 (8.3%)	0.52	0.21
Bilirubin elevation	1 (2.2%)	0	1 (8.3%)	1 (8.3%)	0.38	0.21
PVT	0	0	0	0	N/A	N/A
Adverse events requiring an intervention	0	0	0	0	N/A	N/A

NOTE. Listed are adverse events, as defined by Common Terminology Criteria for Adverse Events (version 5.0).

Data are expressed as N (%).

GI, gastrointestinal; AST, aspartate aminotransferase; ALT, alanine transaminase; PVT, portal vein thrombosis

Supplemental Table 6. Cost related to treatments in South Korea

Treatment modality	USD ($)
Liver resection	8,082
Radiofrequency ablation (RFA)	2,085
Percutaneous ethanol injection (PEI)	1,640
Liver transplantation	67,142
Transarterial chemoembolization (TACE)	3,165
Cytotoxic chemotherapy	2,465
Radiation therapy	3,653
Metastasectomy	5,806
Transarterial radioembolization (TARE)	22,285
Sorafenib (per 4 weeks)	1,153
Lenvatinib (per 4 weeks)	1,313
Regorafenib (per 4 weeks)	2,182
Nivolumab (per 2 weeks)	1,938
Cabozantinib (per 4 weeks)	20,142
Pembrolizumab (per 3 weeks)	4,426

Supplemental Table 7. Comparison of cost between the TARE group and the resection group

	TARE (n=57)	Resection (n=500)	P value
Follow-up duration, months (interquartile range)	19.0 (10.0–37.1)	41.2 (19.8–63.2)	<0.001
Total cost of all treatments, USD (per patient)			
Mean ± SD	53,541 ± 29,364	16,393 ± 16,885	<0.001
Median (range)	46,531 (18,449–52,861)	8,082 (8,082–17,522)	<0.001
Cost of all treatments, USD (per-patient-per-month)			
Mean ± SD	3,632 ± 2,910	716 ± 1,875	<0.001
Median (range)	2,890 (1,437–4,495)	331 (164–782)	<0.001
Total cost of all additional treatments, USD (per patient)			
Mean ± SD	15,092 ± 29,364	8,311 ± 16,885	0.092
Median (range)	8,082 (0–14,412)	0 (0-9,440)	<0.001
Cost of all additional treatments, USD (per-patient-per-month)			
Mean ± SD	596 ± 901	292 ± 1,228	0.023
Median (range)	296 (0–628)	0 (0–297)	<0.001

1 USD = 1,166.51 KRW

TARE, transarterial radioembolization; SD, standard deviation