Master's Thesis of Medicine

Long-Term Outcomes of Transarterial Radioembolization for Large Single Hepatocellular Carcinoma: A Comparison to Resection

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Abstract

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Introduction: The surgical treatment for large hepatocellular carcinoma (HCC) remains controversial due to a high risk of recurrence after resection. This study aimed to compare long-term outcomes of transarterial radioembolization (TARE) with resection for patients with large HCC.

Methods: This retrospective cohort study included a total of 557 patients who were initially treated with either resection (the resection group, n=500) or TARE (the TARE group, n=57) for large (≥5 cm) single nodular HCC at two tertiary centers in Korea. Patients with major portal vein tumor thrombosis or extrahepatic metastasis were excluded. The primary endpoint was overall survival (OS), and secondary endpoints were time to progression (TTP), time to intrahepatic progression (TTIP), and safety.

Results: The resection group were younger (median, 60 years vs. 69 years) with smaller tumor size (median, 7.0 cm vs. 10.0 cm) (all $P<0.05$). After baseline characteristics were balanced using inverse probability of treatment weighting (IPTW), the TARE group showed comparable OS (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.40–2.43; P=0.97), TTP (HR, 1.10; 95% CI, 0.55–2.20; P=0.80), and TTIP (HR, 1.45; 95% CI, 0.72–2.93; P=0.30) to the

resection group. TARE was not an independent risk for OS (adjusted-HR, 1.04; 95% CI, 0.42-2.59; P=0.93), TTP (adjusted-HR, 0.98; 95% CI, 0.50-1.95; P=0.96), or TTIP (adjusted-HR, 1.30; 95% CI, 0.65-2.58; P=0.46). The TARE group showed shorter hospital stay and fewer adverse events than the resection group.

Conclusion: TARE showed comparable OS, TTP, and TTIP with better safety profile compared to surgical resection for large single nodular HCC.

Keyword : liver cancer, overall survival, time to progression, safety, initial treatment

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Chapter 1. Introduction

1.1. Study Background

Hepatocellular carcinoma (HCC) accounts for most of the liver cancers worldwide and is the leading cause of cancer-related mortality in many countries (*1*). Despite efforts toward risk factor management, early diagnosis, and therapeutic advances, the disease burden of liver cancer continues to mount (*2*).

The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend surgical resection as the treatment of choice for adults with single HCC, especially in case of a size less than 5 cm (*3,4*). For those with a large (>5 cm) single HCC, however, controversies exist on the best treatment option. Large tumor size has proven to be related to poor post-surgical outcomes (*5,6*), high probability of vascular invasion and a poor histological differentiation (*7,8*), with the 5-year disease-free survival rate ranging from 20.0% to 41.3% even after curative resection (*6,9*). Transarterial chemoembolization (TACE) has been investigated as an alternative for large HCC, but a meta-analysis reported the clinical outcome to be worse than that of resection (*10*).

Transarterial radioembolization (TARE) is a novel procedure that delivers microspheres loaded with radioactive isotope ^{90}Y to a target lesion; it has emerged as a less invasive treatment option for HCC (*11*). Previous studies have demonstrated that TARE, compared to TACE, showed a comparable overall survival (OS), a longer time to progression (TTP) and more effective performance in downstaging patients on the liver transplant waiting list (*12,13*). Furthermore, a recent multicenter study by Salem et al. showed that TARE was effective and safe when used as either a bridging therapy or a stand-alone treatment for solitary unresectable HCC of <8 cm (*14*). Unlike TACE, which entails risk for delivering suboptimal doses of chemotherapeutic agents to large HCCs due to the

possibility of leakage into the systemic circulation (*15*), TARE has proven to achieve a sufficiently high dose of radiation to large tumors, thereby resulting in a favorable tumor response (*16,17*). In addition, while TACE has a macroembolic effect, which is the main cause of post-embolization syndrome, TARE rarely occludes large vessels and consequently results in less risk of post-embolization syndrome, fewer adverse events, and shorter hospital stay (*18*). Thus, TARE is expected to be more effective and safer for the treatment of large HCCs than TACE.

1.2. Purpose of Research

This study aimed to compare the long-term outcomes of TARE to those of resection in patients with a large single nodular HCC, with a special interest in whether TARE can be a potential alternative to resection.

Chapter 2. Materials and Methods

2.1. Patients

This was a retrospective cohort study using prospectively established electronic HCC databases from Seoul National University Hospital (Seoul, Korea) and Samsung Medical Center (Seoul, Korea). This study was approved by the institutional review board of each center (No. 2101-093-1189; No. 2021-05-109-001). The requirement for informed consent was waived in this study.

By screening the HCC cohort databases, I identified consecutive adult (≥18 years) patients who were treated with either surgical resection (the resection group) or TARE (the TARE group) as an initial treatment for newly diagnosed large (≥5 cm) single nodular HCC (as determined by radiologic assessment) between January 2012 and December 2020. The decision to whether undergo surgical resection or TARE was made upon each patient's preference after a detailed discussion with a physician. Exclusion criteria were (1) sequential multimodality treatment (e.g. surgical resection following TARE in a prearranged manner), (2) tumor thrombosis involving major portal veins, (3) extrahepatic metastasis, (4) impaired hepatic function (Child-Pugh class B or C), (5) poor performance status graded as Eastern Cooperative Oncology Group performance-status score of 1 or above, and (6) previous other malignancies within two years prior to the initial diagnosis of HCC. Patients with minute satellite lesions around the main nodule or tumor thrombosis involving minor branches of portal vein were included.

Portal vein tumor thrombosis (PVTT) 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*). In this study, patients with Vp1 or Vp2 PVTT were included, whereas those with Vp3 or Vp4 PVTT were excluded.

Liver cirrhosis was diagnosed by radiological and clinical criteria as follows: (i) platelet count of <100,000/mm^3 and a blunted, nodular liver edge accompanied by splenomegaly (>12 cm) and/or (ii) the presence of esophageal or gastric varices, ascites, or hepatic encephalopathy. The albumin–bilirubin grades were calculated using the original formulas (*21*). The American Society of Anesthesiologists (ASA) physical status classification was documented for each patient. Information on the pre–treatment liver imaging studies was also collected. The medical costs for the treatments were obtained from the Health Insurance Review & Assessment Service (HIRA) national patients sample (NPS) data of the South Korean government which includes approximately 3% of the total South Korean population (*22,23*). From the HIRA–NPS data, the claims for treatments (i.e., resection, TARE, radiofrequency ablation, percutaneous ethanol injection therapy, transplantation, TACE, external–beam radiation therapy, and systemic cytotoxic chemotherapy) were extracted. Drug costs were estimated usually 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 above mentioned, and the treatment duration of each patient. The cost of clinical trials was excluded from this analysis.

2.2. Procedures

Surgical resection was performed by surgeons with more than 10 years of experience in liver resection. The type and extent of surgery was determined considering tumor size, location, and underlying liver status.

TARE was conducted by interventional radiologists with more than 10 years of experience in vascular intervention. The selection of microsphere between TheraSphere® (Boston Scientific, Marlborough, MA, USA) and SIR-Spheres® (Sirtex Medical Ltd, Woburn, MA, USA) was generally determined by interventional radiologists' personal preference. Microspheres (TheraSphere® or SIR-Spheres®) impregnated with radioisotope ^{90}Y were delivered through the hepatic artery to the tumors with preferential blood flow according to standardized techniques (*25,26*). The dose calculation, as recommended by the manufacturers, was based on the Medical Internal Radiation Dose (MIRD) dosimetry for TheraSphere® and partition dosimetry for SIR-Spheres®, respectively. For TheraSphere®, TARE was not applied if the estimated lung dose exceeded 30 Gy by MIRD dosimetry. For SIR-Spheres®, TARE was not done if the estimated lung dose was higher than 25 Gy by partition model. When radiation segmentectomy is feasible, ^{90}Y microspheres were injected at the segmental hepatic artery. If not, lobar treatment was performed. When there was accessory gastric artery, right gastric artery, or hepatic falciform artery originating from left hepatic artery, coil embolization was performed prior to radioembolization. As long as estimated lung dose is less than upper limit (30 Gy for TheraSphere®, 25 Gy for SIR-spheres®), boosted radioembolization (mean target tissue dose > 150 Gy) was tried (*16*).

2.3. Endpoints and Assessments

The primary endpoint was OS. OS was measured from treatment to death from any cause. Secondary endpoints were

TTP and time to intrahepatic progression (TTIP), which were measured from the treatment to any tumor progression and to intrahepatic tumor progression, respectively, according to HCC-specified modified Response Evaluation Criteria in Solid Tumors criteria (*27*). After initial treatment, tumor progression was monitored every three months from baseline for 24 months and then every three to six months using either dynamic liver computed tomography (CT) or magnetic resonance imaging (MRI) with serum tumor markers (i.e., serum alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II). If the tumor markers rose or the arterially hyperenhancing portion of the treated tumor showed an increase in size after TARE, I regarded the time point of progression as the date when such changes were first identified on an imaging study. In the measurement of TTP and TTIP, patients were censored at the date of an additional treatment without radiological evidence of disease progression or at the time of last follow-up, whichever came first. Adverse events according to the Common Terminology Criteria for Adverse Events version 5.0 were evaluated up until 30 days after the initial treatment. Adverse events for which a radiologic or surgical intervention was required and hospital length of stay for the initial treatment were assessed. Time interval and modality of follow-up imaging studies were collected.

2.4. Statistical Analysis

Patients' baseline characteristics were compared using the χ^2 test or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables.

Inverse probability of treatment weighting (IPTW) was applied to balance the baseline characteristics. Propensity scores of the initial treatment modality (TARE or resection) were calculated by fitting a logistic regression model including all baseline characteristics variables (age, sex, etiology of HCC, presence of liver cirrhosis, ALBI grade, AFP level, presence of tiny satellite nodules, tumor size, extent of lobar involvement, and

extent of PVTT). I performed weight truncation at the 1st and 99th percentiles to avoid the influence of extreme weights and used stabilized weights for IPTW analysis (*28–30*). The balance of baseline characteristics between the two groups was reevaluated after IPTW (*31*).

Using a standard log–rank test, I evaluated the differences in the final outcomes between the groups. I plotted cumulative death rates, cumulative progression rates and cumulative intrahepatic progression rates by the Kaplan–Meier method. Unadjusted hazard ratios (HRs) were estimated using the Cox proportional hazards model. Comparative analyses mainly used the IPTW–adjusted population but also employed the crude population when it came to additional treatment modalities and follow–up imaging modalities. To identify independent predictors of death, tumor progression, and intrahepatic tumor progression, univariable and multivariable logistic regression analyses were performed.

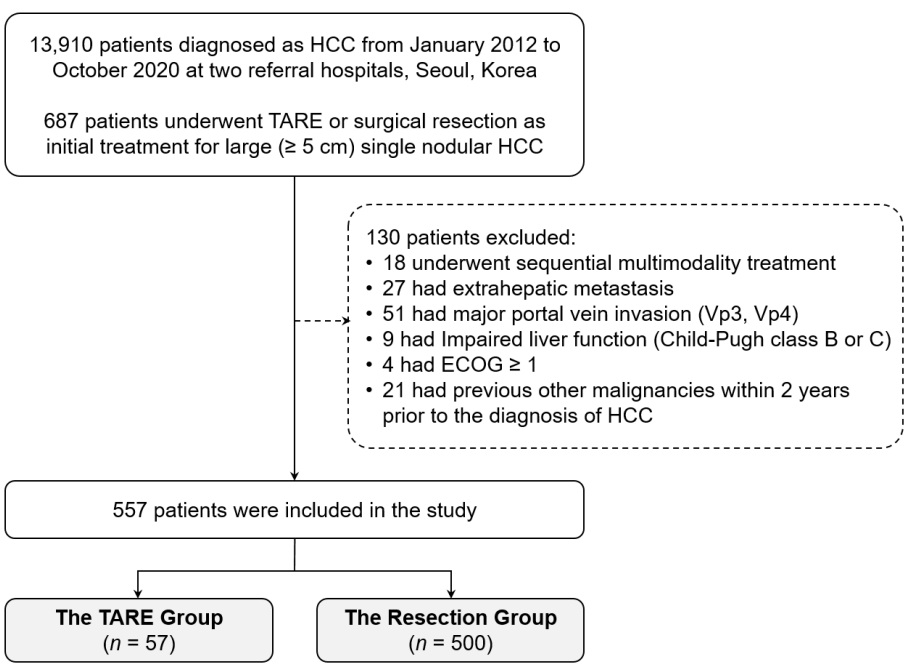
Variables with $P<0.10$ in univariable analysis were used in multivariable analysis. A weighted Cox proportional hazards model was used to identify independent risk factors for the endpoints. All statistical analyses were performed with SPSS software (SPSS version 25.0; SPSS, Chicago, IL, USA) and the R statistical programming environment (version 4.1.1; R development Core Team, Vienna, Austria, http://www.R–project.org), with $P<0.05$ indicating statistical significance.

Chapter 3. Results

3.1. Study Population

A total of 687 patients received either TARE or surgical resection for newly diagnosed large (≥5 cm) single nodular HCC between January 2012 and October 2020. Among them, 130 patients were excluded due to sequential multimodality treatment (n=18), the presence of extrahepatic metastasis (n=27), Vp3 or Vp4 PVTT (n=51), impaired hepatic function (Child-Pugh class B or C) (n=9), an Eastern Cooperative Oncology Group performance-status score of 1 or above (n=4), or previous history of other malignancies within two years prior to the diagnosis of HCC (n=21). Total 557 patients (57 for the TARE group, 500 for the resection group) were eligible for the analysis [Figure 1].

[Figure 1] Flow chart of the study population.



The TARE group were older, had worse physical status (higher proportions of ASA classification 3), had larger tumors, and had more Vp2 PVTT than the resection group [Table 1].

[Table 1] Baseline Characteristics of the Study Population

	TARE (n=57)	Resection (n=500)	P value
Age, years	69.0 (60.0–77.0)	60.0 (52.0–68.0)	<0.001
Age, N (%)			<0.001
< 60 years	13 (22.8%)	246 (49.2%)	
≥ 60 years	44 (77.2%)	254 (50.8%)	
Sex, N (%)			0.52
Female	7 (12.3%)	83 (16.6%)	
Male	50 (87.7%)	417 (83.4%)	
ASA classification			0.106
1	3 (5.3%)	41 (8.2%)	
2	26 (45.6%)	285 (57.0%)	
3	28 (49.1%)	174 (34.8%)	
ASA classification			0.047
1 or 2	29 (50.9%)	326 (65.2%)	
3	28 (49.1%)	174 (34.8%)	
Etiology, N (%)			0.21
HBV	33 (57.9%)	335 (67.0%)	
HCV	3 (5.3%)	31 (6.2%)	
Alcohol	8 (14.0%)	41 (8.2%)	
NASH	0 (0.0%)	15 (3.0%)	
Unknown	13 (22.8%)	78 (15.6%)	
Liver cirrhosis, N (%)	22 (38.6%)	151 (30.2%)	0.25
ALBI grade, N (%)			0.30
1	45 (78.9%)	426 (85.2%)	
≥ 2*	12 (21.1%)	74 (14.8%)	
AFP, ng/mL	7.3 (4.3–132.4)	15.4 (4.2–774.4)	0.19
AFP, N (%)			0.09
< 400 ng/mL	47 (82.5%)	355 (71.0%)	
≥ 400 ng/mL	10 (17.5%)	145 (29.0%)	
Tiny satellite nodules, N (%)			0.33
Absent	53 (93.0%)	478 (95.6%)	

Present	4 (7.0%)	22 (4.4%)	
Tumor size, cm	10.0 (7.5–11.3)	7.0 (5.5–9.2)	<0.001
Tumor size, N (%)			<0.001
< 8 cm	17 (29.8%)	306 (61.2%)	
≥ 8 cm	40 (70.2%)	194 (38.8%)	
Lobar involvement, N (%)			0.04
Unilobar	41 (71.9%)	420 (84.0%)	
Bilobar	16 (28.1%)	80 (16.0%)	
Level of PVTT			0.02
Vp0 (absent)	51 (89.5%)	467 (93.4%)	
Vp1	1 (1.8%)	23 (4.6%)	
Vp2	5 (8.8%)	10 (2.0%)	
Vp			0.01
0–1	52 (91.2%)	490 (98.0%)	
2	5 (8.8%)	10 (2.0%)	

*One patient in resection group had ALBI grade 3.

Data are provided in N (%) or median (interquartile range).

TARE, transarterial radioembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; ALBI, albumin–bilirubin; AFP, alpha–fetoprotein; ASA, American Society of Anesthesiologists; PVTT, portal vein tumor thrombosis; 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.

Among the TARE group, 45 patients were treated with TheraSphere® and 12 patients were treated with SIR-Spheres®. The mean total radiation activity administered was higher in TheraSphere® cases (mean ± standard deviation, 5.12 ± 2.21 GBq; median, 4.75 GBq; range, 1.35-11.75 GBq) than in SIR-Spheres® cases (mean ± standard deviation, 2.86 ± 1.10 GBq; median, 3.35 GBq; range, 1.00-4.00 GBq) (P=0.001). The mean target tissue dose of TheraSphere® cases was 286.5 ± 177.2 Gy (median, 226.0 Gy; range, 84.0-780.0 Gy) and the mean tumor dose of SIR-Spheres® cases was 231.9 ± 84.9 Gy (median, 202.0 Gy; range, 144.4-413.7 Gy). The differences in the baseline characteristics between the TARE group and the resection group were balanced to a statistically insignificant level by means of IPTW, with all listed covariates having a standardized mean difference under 0.25. There were differences in pre-treatment liver imaging tools between the TARE group (28.1% patients were assessed only by CT, 71.9% including MRI) and the resection group (0.6% patients were assessed only by CT, 99.4% including MRI) (P<0.001). The imaging interval at which the tumor progression was detected (median, 2.8 vs. 2.9 months; P=0.75) and imaging modalities (CT, 58.8% vs. 50.4%; MRI, 41.2% vs. 39.3%; P=0.87) were similar between the TARE group and the resection group [Table 2].

[Table 2] Imaging Studies: Modalities and 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%)	

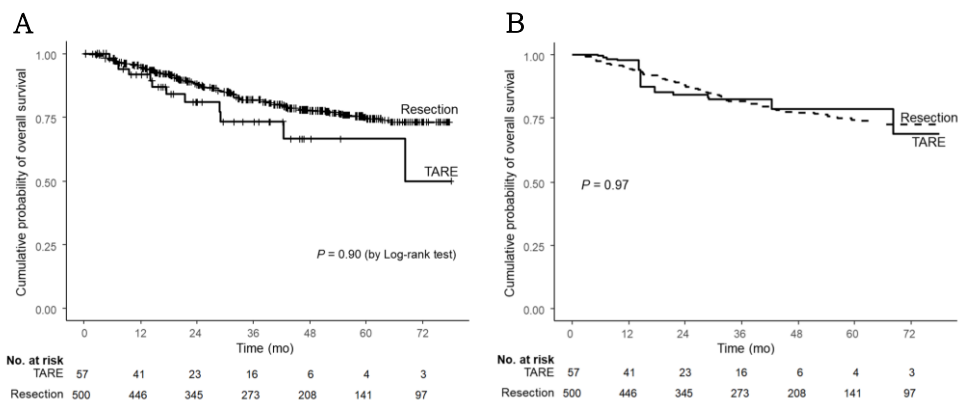
Data are presented as N (%) or median (interquartile range).
CT, computed tomography; MRI, magnetic resonance imaging.

3.2. Overall Survival

During a median follow-up period of 38.4 months, 12 of 57 (21.1%) patients in the TARE group and 102 of 500 (20.4%) patients in the resection group died. The cumulative survival rates at 1, 3, and 5 years were 91.8%, 73.3%, and 66.6%, respectively, in the TARE group and 94.9.
%, 81.8%, and 74.9%, respectively, in the resection group. OS did not significantly differ between the two groups (P=0.90 by log-rank test) [Figure 2A].

After IPTW, the TARE group still showed comparable OS to the resection group (HR, 0.98; 95% confidence interval [CI], 0.40–2.43; P=0.97) [Figure 2B]. In the multivariable analysis, TARE was not an independent risk factor of death (adjusted HR [aHR], 1.04; 95% CI, 0.42–2.59; P=0.93) after adjustment for ASA classification, liver cirrhosis, albumin-bilirubin grade, presence of satellite nodules, and level of PVTT (Vp2 vs. no or Vp1 PVTT). Albumin-bilirubin grade 2 or above (aHR, 1.98; 95% CI, 1.02–3.83; P=0.04) remained significantly associated with death [Table 3].

[Figure 2] Cumulative probability of overall survival according to treatment groups in crude analysis (A) and after using IPTW (B).



[Table 3] Risk Factor Analysis for Overall Survival

Variable	Univariable Analysis		Multivariable Analysis	
	Hazard ratio 95% CI	P value	Hazard ratio 95% CI	P value
Age ≥ 60 (vs. <60)	0.74 (0.38–1.45)	0.38		
Male (vs. female)	1.22 (0.58–2.58)	0.60		
ASA classification 3 (vs. 1 or 2)	2.64 (1.34–5.21)	0.005	1.95 (0.88–4.32)	0.10
HBV-related	1.23 (0.62–2.43)	0.56		
Liver cirrhosis	2.51 (1.22–5.16)	0.01	1.07 (0.43–2.65)	0.89
ALBI grade ≥2 (vs. 1)	2.60 (1.23–5.49)	0.01	1.98 (1.02–3.83)	0.04
AFP ≥400 ng/mL (vs. <400 ng/mL)	0.80 (0.40–1.60)	0.53		
Satellite nodules	1.47 (0.98–2.20)	0.06	1.29 (0.87–1.90)	0.20
Tumor size ≥8 cm	1.41 (0.63–3.14)	0.40		
Bilobar involvement	1.51 (0.73–3.12)	0.26		
Vp2 (vs. Vp0-1)	1.63 (0.94–2.81)	0.08	1.57 (0.86–2.84)	0.14
TARE (vs. resection)	0.98 (0.40–2.43)	0.97	1.04 (0.42–2.59)	0.93

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

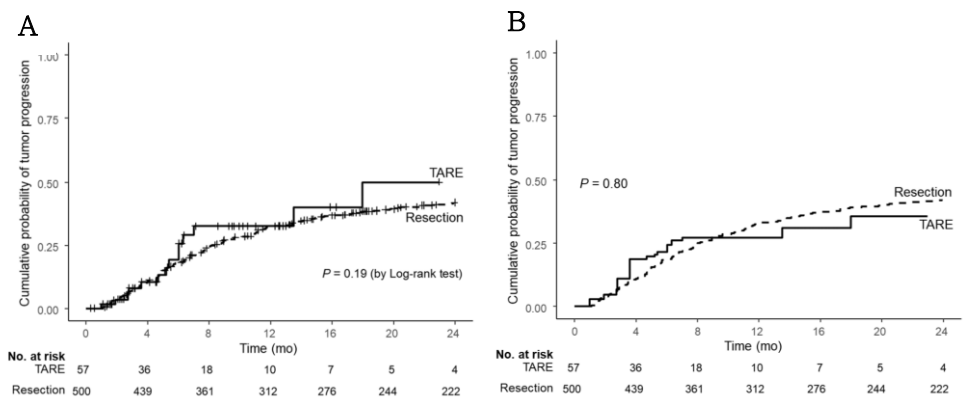
HBV, hepatitis B virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; Vp2, invasion of (or tumor thrombus in) second order branches of the portal vein; Vp0, absence of invasion of (or tumor thrombus in) the portal vein; Vp1, invasion of (or tumor thrombus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

3.3. Time to Progression

The median TTP was 18.0 (interquartile range [IQR], 6.0–34.0) months in the TARE group and 41.8 (IQR, 8.2–not reached) months in the resection group. The cumulative 2-year progression rates were 50.0% in the TARE group and 58.3% in the resection group. The TTP was comparable between the groups (P=0.19) [Figure 3A].

After employing IPTW, there was still no difference in the TTP between the groups (TARE vs. resection: HR, 1.10; 95% CI, 0.55–2.20; P=0.80) [Figure 3B]. In the multivariable regression analysis, TARE over surgery was not an independent risk factor of tumor progression (aHR, 0.98; 95% CI, 0.50–1.95; P=0.96). The presence of satellite nodules (aHR, 1.40; 95% CI, 1.01–1.95; P=0.04) and level of PVTT (Vp2 PVTT vs. no or Vp1 PVTT: aHR, 1.67; 95% CI, 1.16–2.41; P=0.006) remained significantly associated with tumor progression [Table 4].

[Figure 3] Cumulative probability of time to progression according to treatment groups in crude analysis (A) and after using IPTW (B).



[Table 4] 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

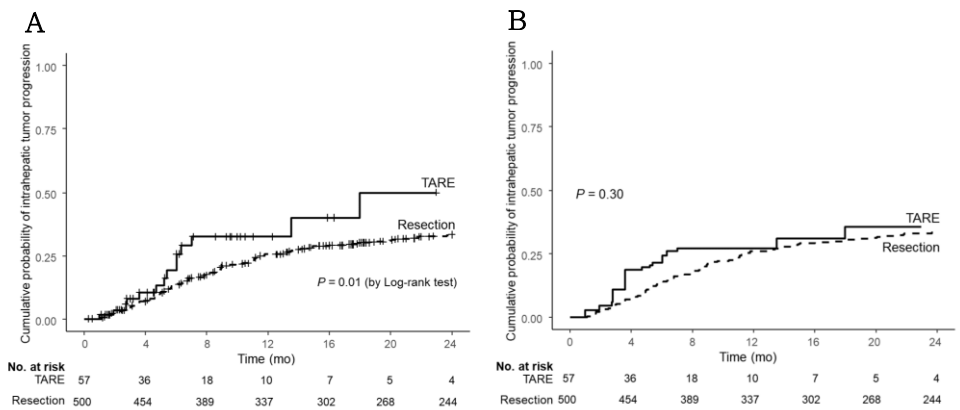
HBV, hepatitis B virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; Vp2, invasion of (or tumor thrombus in) second order branches of the portal vein; Vp0, absence of invasion of (or tumor thrombus in) the portal vein; Vp1, invasion of (or tumor thrombus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

3.4. Time to Intrahepatic Progression

During follow-up, intrahepatic tumor progression was observed in 17 of 57 (29.8%) patients in the TARE group and 244 of 500 (48.8%) in the resection group. The median TTIP was 18.0 (IQR, 6.0-34.0) months in the TARE group and 72.2 (IQR, 11.3-not reached) months in the resection group. The cumulative 2-year intrahepatic progression rates were 50.0% in the TARE group and 33.4% in the resection group. The TTIP was shorter in the TARE group than in the resection group (P=0.01) [Figure 4A].

In the IPTW adjusted population, there was no difference in the TTIP between the groups (TARE vs. resection: HR, 1.45; 95% CI, 0.72-2.93; P=0.30) [Figure 4B]. In the multivariable regression analysis, TARE over surgery was not an independent risk factor of intrahepatic tumor progression (aHR, 1.30; 95% CI, 0.65-2.58; P=0.46) after adjustment for level of PVTT (Vp2 PVTT vs. no or Vp1 PVTT: aHR, 1.72; 95% CI, 1.18-2.50; P=0.005) [Table 5].

[Figure 4] Cumulative probability of time to intrahepatic progression according to treatment groups in crude analysis (A) and after using IPTW (B).



[Table 5] 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.

3.5. Further Treatment

Patients who experienced disease progression underwent additional treatment with multidisciplinary modalities including additional TARE, TACE, radiofrequency ablation, percutaneous ethanol injection, surgical resection of intrahepatic or extrahepatic lesions, liver transplantation, external beam radiation therapy, and systemic therapy such as sorafenib [Table 6]. There were 26 patients (all 26 were in the TARE group) who received additional treatment in order to better control the index lesion in spite of no radiological evidence of tumor progression. Of the 26 patients, 15 patients experienced disease progression and received further treatment. The TARE group underwent more additional treatments (median, 2.0; IQR, 0.0–3.0) than the resection group (median, 0.0; IQR 0.0–2.0) (P=0.002).

[Table 6] Summary of Additional Treatment Modalities

	TARE (n=57)	Resection (n=500)	P value
Additional treatment before tumor progression			
TARE, times (%)	2 (3.5%)	0 (0.0%)	0.010
TACE, times (%)			<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, times (%)	9 (15.8%)	0 (0.0%)	<0.001
Liver transplantation, times (%)	1 (1.8%)	0 (0.0%)	0.10
Intrahepatic RT, times (%)	1 (1.8%)	0 (0.0%)	0.10
Systemic therapy, times (%)	1 (1.8%)	0 (0.0%)	0.10
Total number of additional treatment before tumor progression*, times (%)			<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, times (%)	4 (7.0%)	2 (0.4%)	<0.001
TACE, times (%)			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 (%)			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, times (%)	0 (0.0%)	3 (0.6%)	>0.99
Hepatic resection, times (%)			0.65
1	0 (0.0%)	11 (2.2%)	
2	0 (0.0%)	1 (0.2%)	
Metastasectomy, times (%)			0.70
1	1 (1.8%)	19 (3.8%)	

2–4	1 (1.8%)	12 (2.4%)	
Liver transplantation, times (%)	0 (0.0%)	9 (1.8%)	0.61
Intrahepatic RT, times (%)			0.13
1	2 (3.5%)	23 (4.6%)	
2	1 (1.8%)	0 (0.0%)	
Extrahepatic RT, times (%)			0.42
1–2	3 (5.3%)	38 (7.6%)	
≥ 3	0 (0.0%)	11 (2.2%)	
Systemic therapy, times (%)	11 (19.3%)	86 (17.2%)	0.83
Number of additional treatment after tumor progression per patient†, times (%)			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.

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

3.6. Safety

Overall, adverse events were reported more frequently in the resection group (100%) than in the TARE group (43.9%). All patients in the resection group were graded as having abdominal pain of grade 3 or 4 and routinely received intravenous patient-controlled analgesia using opioids for acute postoperative pain control. Apart from abdominal pain, ascites, fever, aspartate transaminase elevation, alanine transaminase elevation, and bilirubin elevation were reported more frequently in the resection group [Table 7].

Most patients in the resection group showed abnormal liver enzyme levels, which returned to baseline levels except in one patient with liver failure. None of the patients in the TARE group and 16 out of 484 patients (3.2%) in the resection group experienced adverse events requiring radiological or surgical intervention (P=0.39). The hospital stay duration was significantly shorter in the TARE group (median, 3 days; IQR 3-4 days) than in the resection group (median, 12 days; IQR, 11-16 days) (P <0.001).

[Table 7] Safety Assessment

Adverse event	TARE (n=57)		Resection (n=500)		P value	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Overall incidence	25 (43.9%)	5 (8.8%)	500 (100%)	500 (100%)	<0.001	<0.001
Ascites	0	0	37 (7.4%)	5 (1.0%)	0.024	1.00
Fever	3 (5.3%)	0	104 (20.8%)	1 (0.2%)	0.008	1.00
Nausea	7 (12.3%)	0	54 (10.8%)	3 (0.6%)	0.91	1.00
Vomiting	5 (8.8%)	0	33 (6.6%)	1 (0.2%)	0.58	1.00
Abdominal pain	15 (26.3%)	3 (5.3%)	500 (100%)	500 (100%)	<0.001	<0.001
Biliary anastomotic leak	0	0	14 (2.8%)	9 (1.8%)	0.38	0.61
Wound complication	0	0	28 (5.6%)	3 (0.6%)	0.10	1.00
Dyspnea	0	0	14 (2.8%)	5 (1.0%)	0.38	1.00
GI hemorrhage	0	0	6 (1.2%)	1 (0.2%)	1.00	1.00
AST elevation	4 (7.0%)	1 (1.8%)	488 (97.6%)	269 (53.8%)	<0.001	<0.001

ALT elevation	3 (5.3%)	1 (1.8%)	481 (96.2%)	248 (49.6%)	<0.001	<0.001
Bilirubin elevation	2 (3.5%)	1 (1.8%)	350 (70.0%)	37 (7.4%)	<0.001	0.16
PVT	0	0	15 (3.0%)	5 (1.0%)	0.39	1.00
Adverse events requiring an intervention	0	N/A	16 (3.2%)	N/A	0.39	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

3.7. Subgroup Analysis of the TARE group

The TheraSphere® group (n=45) and SIR-Spheres® group (n=12) showed no significant differences in overall survival (2-year survival rates, 82.7% vs. 80.0%; P=0.4), tumor progression (cumulative 2-year progression rates, 51.5% vs. 43.1%; P=0.9), and intrahepatic tumor progression (cumulative 2-year intrahepatic progression rates, 51.5% vs. 43.1%; P=0.9). The admission days for the TARE was similar between both types of ^{90}Y microspheres (median, 3 vs. 3 days; IQR 3-4 vs. 3-4 days; range 2-13 vs. 3-6 days for TheraSphere® vs. SIR-Spheres®, respectively; P=0.99). Overall adverse events were similar in both groups, while mild nausea and vomiting was reported more frequently in the SIR-Spheres group (nausea 6.7% vs. 33.3%; P=0.03) (vomiting 2.2% vs. 33.3%; P=0.006) [Table 8].

[Table 8] Safety Assessment of the 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

3.8. Cost of Treatment

When I analyzed the cost of initial and additional treatments, the cost of TARE was the secondly highest following liver transplantation among radiological and surgical treatments for HCC [Table 9].

[Table 9] Cost Related to Treatments in South Korea

Treatment modality	Cost (KRW)
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
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

The TARE was 2.8-fold more expensive than surgical resection (KRW 29,065,657 vs KRW 10,541,110). The TARE group showed significantly higher overall cost of treatment (mean, KRW 69,831,920 vs. KRW 21,380,898; P<0.001) (mean, KRW 4,737,109 vs. KRW 933,857 per-patient-per-month; P<0.001) and higher cost of additional treatment (mean, KRW 777,345 vs. KRW 380,847 per-patient-per-month; P=0.023) than the resection group [Table 10].

[Table 10] Comparison of Cost between the TARE group and the Resection group

	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
Total cost of all treatments, KRW (per patient)			
Mean±SD	69,831,920± 38,298,584	21,380,898± 22,022,599	<0.001
Median (range)	60,688,987 (24,062,477-68,945,016)	10,541,110 (10,541,110-22,853,419)	<0.001
Cost of all treatments, KRW (per-patient-per-month)			
Mean±SD	4,737,109± 3,795,426	933,857± 2,445,506	<0.001
Median (range)	3,769,340 (1,874,236-5,862,694)	431,713 (213,900-1,019,939)	<0.001
Total cost of all additional treatments, KRW (per patient)			
Mean±SD	19,684,043± 38,298,584	10,839,788± 22,022,599	0.092
Median (range)	10,541,110 (0-18,797,139)	0 (0-12,312,309)	<0.001
Cost of all additional treatments, KRW (per-patient-per-month)			
Mean±SD	777,345± 1,175,147	380,847± 1,601,644	0.023
Median (range)	386,064 (0-819,082)	0 (0-387,368)	<0.001

Chapter 4. Discussion

When retrospectively compared to resection, TARE showed comparable treatment outcomes in terms of OS, TTP, and TTIP to surgical resection when applied as an initial treatment for a large single nodular HCC in patients with favorable hepatic function and performance status. TARE had benefits over surgical resection when accounting for the length of hospital stay and the incidence of adverse events. However, the TARE group underwent more additional treatments than the resection group.

TARE, when compared to external radiation therapy, can deliver microspheres loaded with a high-energy radioactive particle ^{90}Y closer to the target lesion and therefore enables high tumoricidal doses while sparing adjacent liver parenchyma (*32*). Immune activation at the local tumor microenvironment and systemic level is thought to mediate a delayed and sustained clinical response despite the short half-life of ^{90}Y (*33*). Although previous studies have discussed the role of TARE as a "downsizing" therapy that allows patients with unresectable HCC to consider sequential resection or transplantation (*13,34*), few studies have evaluated the effectiveness of TARE as a curative treatment modality for a single HCC. This study suggests TARE as a potential alternative to surgical resection in a subgroup of patients with resectable single large HCC. Even though the TARE group were older (median, 69 vs. 60 years), more with severe systemic disease (ASA 3), and tended to have more advanced disease (i.e., larger tumor size, more bilobar involvement, and more Vp2 PVTT) than the resection group, the clinical outcomes were similar.

The risk of postoperative hepatic decompensation is a major concern in planning surgical resection of HCC, and such concern increases when it comes to a larger tumor, as the remaining liver volume is relatively smaller (*35,36*). In addition, large tumors are associated with a higher incidence of tumor

recurrence, and thus remnant liver volume and function are important factors when deciding further treatment (*8*). TACE, a less invasive modality compared to surgical resection, has been attempted in treating patients with large HCC. However, a meta-analysis study reported the outcomes of TACE were even worse than surgical resection for patients with solitary large HCC, though it set aside the risks of post-embolization syndrome or aggravation of liver function following repetitive treatment (*10*). TARE is also advantageous in preserving residual liver volume by inducing hypertrophy of the untreated lobe, which is associated with hypotrophy of the treated hepatic lobe (*37-39*); this enables more patients to receive further treatment if needed. The fact that no patient in the TARE group suffered from a serious adverse event in our study emphasizes the safety benefits of TARE, which compensate for the high expense of the procedure and costs for sequential treatments.

The percentage of patients having Vp2 PVTT was higher in the TARE group than the resection group, and Vp2 PVTT over no or Vp1 PVTT was found to be associated with shorter TTIP in multivariable analysis. This could provide an explanation for the benefit the resection group had over the TARE group in terms of TTIP, evaluated by log-rank test before applying IPTW. The equivalence in OS despite the difference in TTIP in the crude analysis may be partially attributed to the effects of additional treatment.

The TARE group underwent more additional treatments than the resection group, however this difference was led by additional treatment performed because of difficult distinction between suspected residual lesion and treatment-related hyperemia (number of patients received additional treatment before tumor progression, 26 vs. 0 for the TARE group and the resection group, respectively; $P<0.001$). In fact, the TARE group showed comparable time to progression and time to intrahepatic progression after IPTW.

The TARE group were older and had poorer baseline physical status (i.e., more frequent ASA classification 3) and higher proportion of unfavorable tumor characteristics than the resection group. The greatest merit of TARE may be that it can

be an effective alternative treatment for high-risk surgical patients due to the remnant future liver and overall medical conditions. This is supported by the result of the present study in which the TARE group had fewer adverse events.

TARE was 2.8-fold more expensive than surgical resection in South Korea (USD 22,285 vs USD 8,082). In addition, the TARE group received more additional treatments and also showed higher cost of additional treatment compared to the resection group (mean, USD 596 vs. USD 292 per-patient-per-month; P=0.023). Thus, the TARE group had significantly higher overall cost of treatment than the surgical resection group (mean, USD 53,541 vs. USD 16,393; P<0.001) (mean, USD 3,632 vs. USD 716 per-patient-per-month; P<0.001) and the TARE might be less cost-effective than surgical resection for large HCC. Nevertheless, TARE can provide comparable outcomes with fewer side effects in relatively high-risk surgical patients. However, given the retrospective nature of this study, future prospective study is warranted to investigate quality of life of treated patients comprehensively.

Additionally, 28.1% of the TARE group were evaluated only by CT before treatment, while 99.4% of the resection group were underwent liver MRI. This tendency might lead the TARE group to be classified as better stage than actual condition due to difference in sensitivity to detect nodules between CT and MRI, giving disadvantage to the TARE group in comparing the outcomes. Nevertheless, the TARE group showed comparable overall survival, time to progression, and time to intrahepatic progression after IPTW in this study.

The TARE group showed comparable treatment outcomes and fewer adverse events compared to the resection group despite worse ASA classification and older age. If the ASA classification or the performance status is poor, TARE, which has a lower risk of side effects than surgery, would be recommended.

There were no significant differences in treatment outcomes, the length of hospital stay, and overall adverse events between the subgroups classified according to the spheres used for TARE. The results indicate that the TheraSphere® group and

SIR-Spheres® group could be reasonably pooled in the analyses mentioned above.

This study has some limitations. First, there can be debate on evaluation of radiological tumor response to TARE; therapy-induced tumor necrosis or fibrosis is not exactly reflected in tumor size (*40*), and the combined effects of embolization and radiation-induced lesional and perilesional changes can be more variable than in TACE (*41*). However, I used strictly predefined criteria for determining the point of disease progression and censoring the patients in measuring TTIP and TTP. Second, this study was retrospectively performed, and there were some notable differences in the baseline profile between the groups. The differences were balanced to some extent by combining IPTW and Cox-proportional hazards regression models (*42*). Third, because the TARE group consisted of only the patients who were found to be eligible for TARE in a pretreatment simulation study, the outcomes of the group may be worse in an intention-to-treat analysis. However, the same is the case with the resection group since those with a higher risk for resection would have been likely to choose other modality for their initial treatment. Fourth, owing to the operator-dependent nature of surgical resection and TARE, further studies are needed to assure the generalizability of the results of this study, which was conducted based on the data from two referral centers with a lot of experience in both treatment modalities. Finally, though a comparison with external charged-particle radiotherapy (such as proton beam therapy) may be helpful in more extensive understanding of the potential of selective radiation therapy in treating large single nodular HCCs (*43*), a practical application of external charged-particle radiotherapy is hampered due to the small number of treatment facilities and the high expense of establishing them. This study focused on TARE, a new modern radiotherapy with relatively high accessibility (*44*).

In conclusion, this study suggests TARE as a possible alternative to surgical resection in patients with large single nodular HCC, with similar efficacy in terms of OS, TTP, and TTIP. Moreover, the TARE group had significantly shorter

hospital stay and a lower tendency to serious adverse events requiring intervention compared to the resection group. Randomized clinical trials involving larger number of patients are needed to assess outcomes in a longer perspective.

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초 록

서론: 거대 간세포암종에 대한 절제술은 높은 재발율로 인해 논란이 있다. 본 연구는 거대 간세포암종 환자들에서 경동맥 방사선색전술과 절제술의 장기적 예후를 비교하고자 하였다.
연구 방법: 본 후향적 코호트 연구는 한국의 두 삼차 의료기관에서 거대(5 cm 이상) 단일 결절형 간세포암종에 대해 절제술(절제술군, 500명)이나 경동맥 방사선색전술(색전술군, 57명)을 초치료로 시행받은 557명의 환자를 대상으로 하였다. 주간문맥 혈전이나 간외 전이를 동반한 환자들은 제외되었다. 일차평가변수는 전체생존기간이었고, 이차평가변수는 종양 진행까지의 시간, 간내 종양 진행까지의 시간, 안전성이었다.
연구 결과: 절제술군이 색전술군에 비해 더 나이가 적었고(중앙값 60세 대 69세), 종양 크기가 더 작았다(중앙값 7 cm 대 10 cm) (모두 P<0.05). 역확률가중치를 적용하여 기저 특성을 보정하였을 때, 색전술군은 절제술군과 대비해 유사한 전체생존기간(위험비 0.98, 95% 신뢰구간 0.40–2.43, P=0.92), 종양 진행까지의 시간(위험비 1.10, 95% 신뢰구간 0.55–2.20, P=0.80), 간내 종양 진행까지의 시간(위험비 1.45, 95% 신뢰구간 0.72–2.93, P=0.30)을 보였다. 경동맥 방사선색전술은 전체생존기간(보정 위험비 1.04, 95% 신뢰구간 0.42–2.59, P=0.93), 종양 진행까지의 시간(보정 위험비 0.98, 95% 신뢰구간 0.50–1.95, P=0.96), 간내 종양 진행까지의 시간(보정 위험비 1.30, 95% 신뢰구간 0.65–2.58, P=0.46)에 있어 독립된 위험 인자가 아니었다. 색전술군이 절제술군에 비해 더 짧은 입원기간과 더 적은 위해사건을 보였다.
결론: 거대 단일 결절형 간세포암종에서 경동맥 방사선색전술은 수술적 절제와 비교하여 유사한 전체생존기간, 종양 진행까지의 시간, 간내 종양 진행까지의 시간을 보였고 안전성 면에서 우월했다.

주요어 : 간암, 전체생존기간, 종양 진행까지의 시간, 안전성, 초치료
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