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

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The surgical treatment for large hepatocellular carcinoma (HCC) remains controversial because of 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 557 patients who were initially treated with either resection ($n = 500$) or TARE ($n = 57$) for large (≥ 5 cm), single nodular HCC at 2 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 was younger (median, 60 vs. 69 y) and had a smaller tumor size (median, 7.0 vs. 10.0 cm) (all $P < 0.05$). After baseline characteristics were balanced using inverse-probability-of-treatment weighting, the OS (hazard ratio [HR], 0.98; 95% 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; $P = 0.30$) of the TARE group was comparable 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 had a shorter hospital stay and fewer adverse events than the resection group. **Conclusion:** Compared with surgical resection for large single nodular HCC, TARE showed a comparable OS, TTP, and TTIP and a better safety profile.

Key Words: liver cancer; overall survival; time to progression; safety; initial treatment

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 when the size is 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 postsurgical outcomes (*5,6*), high probability of vascular invasion, and poor histologic differentiation (*7,8*), with the 5-y 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 metaanalysis reported the clinical outcome to be worse than that of resection (*10*).

Transarterial radioembolization (TARE) is a novel procedure that delivers microspheres loaded with the 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 with 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 a solitary unresectable HCC of less than 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, whereas TACE has a macroembolic effect, which is the main cause of postembolization syndrome, TARE rarely occludes large vessels and consequently results in less risk of postembolization syndrome, fewer adverse events, and a shorter hospital stay (*18*). Thus, TARE is expected to be more effective and safer for the treatment of large HCCs than is TACE.

This study aimed to compare the long-term outcomes of TARE with 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.

MATERIALS AND METHODS

Patients

This was a retrospective cohort study using prospectively established electronic HCC databases from 2 referral centers in Seoul, Korea. This study was approved by the institutional review board of each center (approvals 2101-093-1189 and 2021-05-109-001). The requirement for informed consent was waived.

By screening the HCC cohort databases, we identified consecutive adult (≥18 y) patients who underwent either surgical resection or TARE 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 on whether to undergo surgical resection or TARE was made according to each patient's preference after a detailed discussion with a physician. Exclusion criteria were sequential multimodality treatment (e.g., surgical resection after TARE in a prearranged manner), tumor thrombosis involving major portal veins (right/left portal vein or main trunk portal vein tumor thrombosis [PVTT]) (supplemental methods (19,20); supplemental materials are available at http://jnm.snmjournals.org), extrahepatic metastasis, impaired hepatic function (Child–Pugh class B or C), poor performance status graded as a Eastern Cooperative Oncology Group performance status score of 1 or above, and previous other malignancies within 2 y before the initial diagnosis of HCC. Patients with minute satellite lesions around the main nodule or tumor thrombosis involving minor branches of portal vein (second-order branch [Vp2] or distal to second-order branch [Vp1] PVTT) were included (supplemental methods (19,20)).

Liver cirrhosis was diagnosed by radiologic and clinical criteria as follows: platelet count of less than 100,000/mm^3 and a blunted, nodular liver edge accompanied by splenomegaly (>12 cm) or 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 pretreatment liver imaging tools was also collected. The medical costs for the treatments were obtained from the Health Insurance Review and Assessment Service national patient sample data of the South Korean government (supplemental methods (22–24)).

Procedures

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

TARE was conducted by interventional radiologists with more than 10 y of experience in vascular intervention. The selection of TheraSphere (Boston Scientific) and SIR-Spheres (Sirtex) microspheres was generally left to the interventional radiologists' personal preference. Microspheres impregnated with the radioisotope ^{90}Y were delivered through the hepatic artery to the tumors with preferential blood flow according to standardized techniques (25,26). As recommended by the manufacturers, the dose calculation was based on the MIRD dosimetry for TheraSphere and partition dosimetry for SIR-Spheres. 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 a partition model. When radiation segmentectomy was feasible, ^{90}Y microspheres were injected at the segmental hepatic artery. If not, lobar treatment was performed. When there was an accessory gastric artery, right gastric artery, or hepatic falciform artery originating from the left hepatic artery, coil embolization was performed before radioembolization. As long as the estimated lung dose was less than the upper limit (30 Gy for TheraSphere and 25 Gy for SIR-Spheres), boosted radioembolization (mean target tissue dose > 150 Gy) was tried (16).

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 treatment to any tumor progression and from treatment to intrahepatic tumor progression, respectively, according to HCC-specified modified RECIST criteria (27). After initial treatment, tumor progression was monitored every 3 mo from baseline for 24 mo and then every 3–6 mo using either dynamic liver CT or MRI with serum tumor markers (i.e., serum α-fetoprotein and protein induced by vitamin K absence or antagonist II). All imaging scans were reevaluated by 2 radiologists at each center with more than 5 y of experience. In cases of discordance, an additional third independent experienced radiologist reviewed images and consensus was achieved among the 3 radiologists. If the tumor markers rose or the arterially hyperenhancing portion of the treated tumor grew after TARE, we 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 radiologic 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 until 30 d 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. The time interval and modality of follow-up imaging studies were noted.

Statistical Analysis

Patients' baseline characteristics were compared using the χ^2 test or Fisher exact test for categoric variables and the Mann–Whitney U test for continuous variables. To balance the baseline characteristics, inverse-probability-of-treatment weighting (IPTW) was applied (supplemental methods (28–31)).

Using a standard log-rank test, we evaluated the differences in the final outcomes between the groups. We 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 used mainly the IPTW-adjusted population but also 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 a P value of less than 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 (version 25.0; SPSS) and the R statistical programming environment (version 4.1.1; R development Core Team [http://www.R-project.org]), with a P value of less than 0.05 indicating statistical significance.

RESULTS

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 because of sequential multimodality treatment ($n = 18$), the presence of extrahepatic metastasis ($n = 27$), right/left or main

trunk 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 a previous history of other malignancies within 2 y before the diagnosis of HCC ($n = 21$). In total, 557 patients (57 for the TARE group, 500 for the resection group) were eligible for the analysis (Fig. 1). The TARE group was older and had poorer baseline physical status (higher proportions of ASA classification 3), larger tumors, and more Vp2 PVTT than the resection group (Table 1). Among the TARE group, 45 patients were treated with TheraSphere, and 12 were treated with SIR-Spheres. The mean total radiation activity administered was higher in TheraSphere cases (median, 4.75 GBq; range, 1.35–11.75 GBq) than in SIR-Spheres cases (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 pretreatment 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 mo; $P = 0.75$) 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 (Supplemental Table 1).

Overall Survival

During a median follow-up of 38.4 mo, 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 y 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 2 groups ($P = 0.90$ by log-rank test) (Fig. 2A).

After IPTW, the TARE group still showed comparable OS to the resection group (HR, 0.98; 95% CI, 0.40–2.43; $P = 0.97$) (Fig. 3A). 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 2).

Time to Progression

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

After using IPTW, there was still no difference in the TTP between the groups (TARE vs. resection: HR, 1.10; 95% CI, 0.55–2.20; $P = 0.80$) (Fig. 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 (Supplemental Table 2).
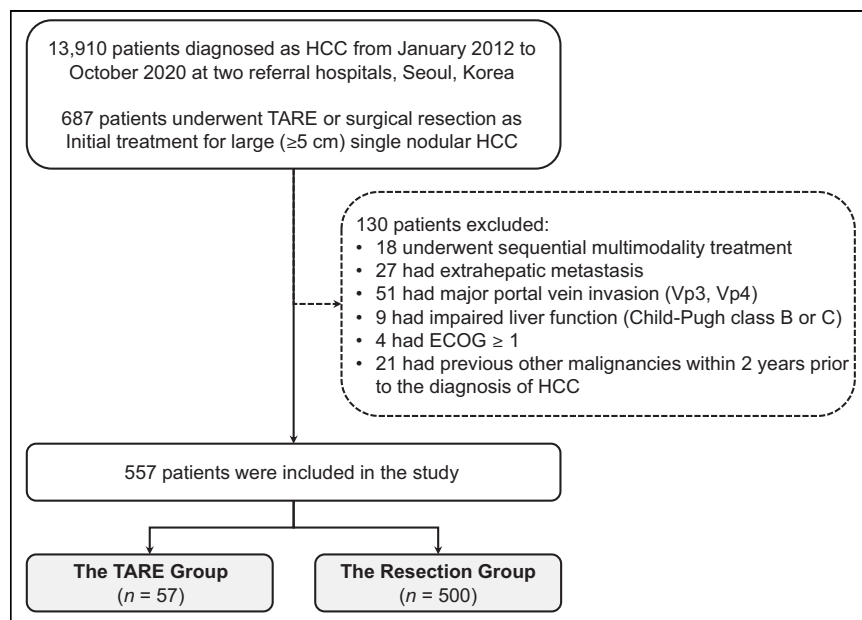
TTIP

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 mo (IQR, 6.0–34.0 mo) in the TARE group and 72.2 mo (IQR, 11.3 mo–not reached) in the resection group. The cumulative 2-y 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 ($P = 0.01$) (Fig. 2C).

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; $P = 0.30$) (Fig. 3C). 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; $P = 0.005$) (Supplemental Table 3).

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 (Supplemental Table 4). There

13,910 patients diagnosed as HCC from January 2012 to October 2020 at two referral hospitals, Seoul, Korea

687 patients underwent TARE or surgical resection as Initial treatment for large (≥5 cm) single nodular HCC

130 patients excluded:
- 18 underwent sequential multimodality treatment
- 27 had extrahepatic metastasis
- 51 had major portal vein invasion (Vp3, Vp4)
- 9 had impaired liver function (Child-Pugh class B or C)
- 4 had ECOG ≥ 1
- 21 had previous other malignancies within 2 years prior to the diagnosis of HCC

557 patients were included in the study

The TARE Group ($n = 57$)
The Resection Group ($n = 500$)

FIGURE 1. Flowchart of study population. ECOG = Eastern Cooperative Oncology Group performance; Vp3 = tumor thrombus in first-order branches of the portal vein; Vp4 = tumor thrombus in the main trunk of the portal vein and/or contralateral portal vein branch to the primarily involved lobe.

TABLE 1
Baseline Characteristics of Study Population

Characteristic	TARE (*n* = 57)	Resection (*n* = 500)	*P*
Age (y)	69.0 (60.0–77.0)	60.0 (52.0–68.0)	< 0.001
Age			< 0.001
< 60 y	13 (22.8%)	246 (49.2%)	
≥ 60 y	44 (77.2%)	254 (50.8%)	
Male sex	50 (87.7%)	417 (83.4%)	0.52
ASA classification			0.047
1 or 2	29 (50.9%)	326 (65.2%)	
3	28 (49.1%)	174 (34.8%)	
Etiology			0.21
Hepatitis B virus	33 (57.9%)	335 (67.0%)	
Hepatitis C virus	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	22 (38.6%)	151 (30.2%)	0.25
ALBI grade			0.30
1	45 (78.9%)	426 (85.2%)	
≥ 2*	12 (21.1%)	74 (14.8%)	
α-fetoprotein (ng/mL)	7.3 (4.3–132.4)	15.4 (4.2–774.4)	0.19
α-fetoprotein			0.09
< 400 ng/mL	47 (82.5%)	355 (71.0%)	
≥ 400 ng/mL	10 (17.5%)	145 (29.0%)	
Tiny satellite nodules	4 (7.0%)	22 (4.4%)	0.33
Tumor size (cm)	10.0 (7.5–11.3)	7.0 (5.5–9.2)	< 0.001
Tumor size			< 0.001
< 8 cm	17 (29.8%)	306 (61.2%)	
≥ 8 cm	40 (70.2%)	194 (38.8%)	
Lobar involvement			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%)	

*One patient in resection group had ALBI grade 3.

NASH = nonalcoholic steatohepatitis; ALBI = albumin–bilirubin; ASA = American Society of Anesthesiologists; Vp0 = absence of tumor thrombus in the portal vein; Vp1 = tumor thrombus in distal to the second order branches of the portal vein, but not of the second order branches; Vp2 = tumor thrombus in second order branches of the portal vein.

Qualitative data are number and percentage; continuous data are median and IQR.

were 26 patients (all 26 were in the TARE group) who received additional treatment to better control the index lesion despite no radiologic 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).

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, the resection group more
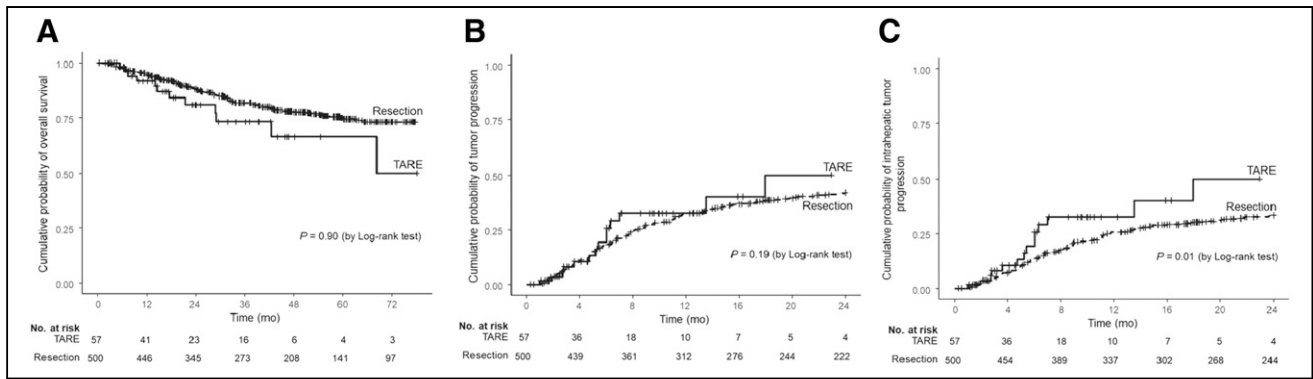
FIGURE 2. Crude analysis: cumulative probability of OS (A), tumor progression (B), and intrahepatic tumor progression (C) according to treatment groups.

frequently reported ascites, fever, aspartate transaminase elevation, alanine transaminase elevation, and bilirubin elevation (Table 3). 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 of 484 patients (3.2%) in the resection group experienced adverse events requiring radiologic or surgical intervention ($P = 0.39$). The hospital stay was significantly shorter in the TARE group (median, 3 d; IQR, 3–4 d) than in the resection group (median, 12 d; IQR, 11–16 d) ($P < 0.001$).

Subgroup Analysis of TARE Group

The TheraSphere group ($n = 45$) and the SIR-Spheres group ($n = 12$) showed no significant differences in OS (2-y survival rates, 82.7% vs. 80.0%; $P = 0.4$), TTP (cumulative 2-y progression rates, 51.5% vs. 43.1%; $P = 0.9$), or TTIP (cumulative 2-y intrahepatic progression rates, 51.5% vs. 43.1%; $P = 0.9$). The admission days for the TARE group were similar between both types of ^{90}Y microspheres (median, 3 vs. 3 d; IQR, 3–4 vs. 3–4 d; range, 2–13 vs. 3–6 d, for TheraSphere vs. SIR-Spheres, respectively; $P = 0.99$). Overall adverse events were similar in both groups, whereas mild nausea and vomiting were more frequent in the SIR-Spheres group (nausea, 6.7% vs. 33.3%; $P = 0.03$) (vomiting, 2.2% vs. 33.3%; $P = 0.006$) (Supplemental Table 5).

Cost of Treatment

When we analyzed the cost of initial and additional treatments, the cost of TARE was one of the highest, second only to liver transplantation, among radiologic and surgical treatments for HCC

(Supplemental Table 6). TARE was 2.8-fold more expensive than surgical resection ($22,285 vs. $8,082) in Korea. The TARE group showed a significantly higher overall cost of treatment (mean, $53,541 vs. $16,393; $P < 0.001$) and a higher cost of additional treatment (mean, $596 vs. $292 per patient per month; $P = 0.023$) than the resection group (Supplemental Table 7).

DISCUSSION

When retrospectively compared with 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 with 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. Our study suggests TARE as a potential alternative to
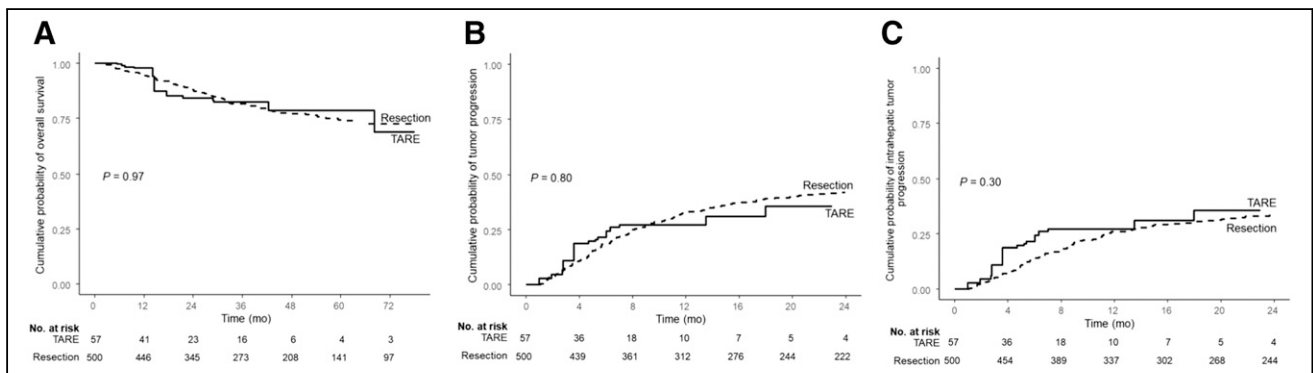
FIGURE 3. After using IPTW: cumulative probability of OS (A), tumor progression (B), and intrahepatic tumor progression (C) according to treatment groups.

TABLE 2
Risk Factor Analysis for OS

Variable	Univariable analysis		Multivariable analysis	
	HR	P	HR	P
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
Hepatitis B virus–related (vs. the others)	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
Albumin–bilirubin 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 or Vp1)	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

Data are with weighted population, using variables with P value under 0.1 at univariable analysis. Data in parentheses are 95% CI.

AFP = α-fetoprotein; Vp0 = absence of tumor thrombus in the portal vein; Vp1 = tumor thrombus in distal to the second-order branches of the portal vein, but not of the second-order branches; Vp2 = tumor thrombus in second-order branches of the portal vein.

surgical resection in a subgroup of patients with resectable single large HCC. Even though the TARE group was older (median, 69 vs. 60 y), had a higher number of patients 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

TABLE 3
Safety Assessment

Adverse event	TARE (n = 57)		Resection (n = 500)		P	
	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
Gastrointestinal 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
Portal vein thrombosis	0	0	15 (3.0%)	5 (1.0%)	0.39	1.00
Adverse events requiring intervention	0	NA	16 (3.2%)	NA	0.39	NA

Listed are adverse events, as defined by Common Terminology Criteria for Adverse Events (version 5.0). Data are number and percentage.

AST = aspartate aminotransferase; ALT = alanine transaminase; NA = not applicable.

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 than surgical resection, has been attempted in treating patients with large HCC. However, a metaanalysis study reported that the outcomes of TACE were even worse than those of surgical resection for patients with solitary large HCC, though the study set aside the risks of postembolization syndrome or aggravation of liver function after 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 had 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 in the resection group, and Vp2 PVTT over no or Vp1 PVTT was found to be associated with a shorter TTIP in multivariable analysis. This finding could explain the benefit the resection group had over the TARE group in terms of TTIP, evaluated by log-rank testing 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.

In the present study, the TARE group underwent more additional treatments after the initial treatment than did the resection group; however, this difference was due to additional treatment performed because of the difficulty of distinguishing between suspected residual lesion and treatment-related hyperemia, as previously reported (40,41): 26 and 0 patients received additional treatment before definite tumor progression in the TARE group and the resection group, respectively. However, TTP and the number of additional treatments after definite tumor progression did not significantly differ between the 2 treatment groups.

When we further analyzed the cost of treatments, TARE was 2.8-fold more expensive than surgical resection in Korea ($22,285 vs. $8,082). In addition, TARE was associated with more additional treatments and a higher cost of additional treatment than was resection (mean, $596 vs. $292 per patient per month; $P = 0.023$). Thus, the TARE group had a significantly higher overall cost of treatment than the surgical resection group (mean, $53,541 vs. $16,393; $P < 0.001$), and TARE might be less cost-effective than surgical resection for large HCC.

On the other hand, the patients in the TARE group were older and had a worse baseline physical status (i.e., more frequent ASA classification 3) and a 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 to surgical resection for high-risk patients because of the future liver remnant and overall medical conditions. This possibility is supported by the results of the present study, in which the TARE group had fewer adverse events and possibly a more favorable posttreatment quality of life. However, given the retrospective nature of this study, a future prospective study is warranted to comprehensively investigate quality of life of treated patients.

Additionally, 28.1% of the TARE group were evaluated only by CT before treatment, whereas 99.4% of the resection group underwent liver MRI. This tendency might lead the TARE group to be misclassified as being in an earlier stage because of the difference in sensitivity of detecting nodules between CT and MRI. Despite this disadvantage of the TARE group in comparing the outcomes, the TARE group showed comparable OS, TTP, and TTIP after IPTW in this study.

In the present study, the TARE group showed comparable treatment outcomes and fewer adverse events than 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.

Our study had some limitations. First, there can be debate on evaluation of radiologic tumor response to TARE; therapy-induced tumor necrosis or fibrosis is not exactly reflected in tumor size (42), and the combined effects of embolization and radiation-induced lesional and perilesional changes can be more variable than in TACE (43). However, we used strictly predefined criteria for determining the point of disease progression and censoring the patients in measuring TTIP and TTP. Second, this study was retrospective, 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 (44). Third, because of the operator-dependent nature of surgical resection and TARE, further studies are needed to ensure the generalizability of the results of our study, which was conducted at 2 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 extensively understanding the potential of selective radiation therapy in treating large single nodular HCCs (45), a practical application of external charged-particle radiotherapy is hampered by the small number of treatment facilities and the high expense of establishing them. Our study focused on TARE, a new modern radiotherapy with relatively high accessibility (46).

CONCLUSION

Our 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 experience serious adverse events requiring intervention than did the resection group. Randomized clinical trials involving larger numbers of patients are needed to assess outcomes in a longer perspective.

DISCLOSURE

KEY POINTS

QUESTION: Is TARE a potential alternative to surgical resection in patients with large single nodular HCC?

PERTINENT FINDINGS: In this retrospective cohort study of newly diagnosed HCC patients with large single nodular tumor, TARE—compared with surgical resection—showed similar OS and TTP and a better safety profile.

IMPLICATIONS FOR PATIENT CARE: TARE can act as a reasonable alternative to surgical resection in a carefully selected group of patients with a large single nodular HCC.

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