Journal of Nuclear Medicine, published on December 9, 2021 as doi:10.2967/jnumed.121.263147

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

Running Title

TARE vs. Resection for Large Single HCC

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Financial Support: The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

ASA, American Society of Anesthesiologists; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; MIRD, Medical Internal Radiation Dose; OS, overall survival; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TTIP, time to intrahepatic progression; TTP, time to progression.

Abstract

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.

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

INTRODUCTION

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 Disease 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 yttrium-90 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.

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.

MATERIALS and METHODS

Patients

This was a retrospective cohort study using prospectively established electronic HCC databases from two referral centers in 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, we 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 (≥5cm) 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 (Vp3 or Vp4 portal vein tumor thrombosis [PVTT]) (Supplementary Methods(*19,20*)), (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 (Vp1 or Vp2 PVTT) were included (Supplementary Methods(*19,20*)).

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 tools 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 (Supplementary Methods(*22-24*)).

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® and SIR-Spheres® was generally determined by interventional radiologists' personal preference. Microspheres (Therasphere® or SIR-Spheres®) impregnated with radioisotope yttrium-90 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 a partition model. When radiation segmentectomy was feasible, yttrium-90 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 prior to 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 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). All imaging scans were re-evaluated by two radiologists at each center with more than 5 years' experience. In cases of discordance, an additional third independent experienced radiologist reviewed images and consensus was achieved among the three radiologists. If the tumor markers rose or the arterially hyperenhancing portion of the treated tumor showed an increase in size 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 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.

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. To balance the baseline characteristics, inverse probability of treatment weighting (IPTW) was applied (Supplementary 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 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.

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 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). 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 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 (Supplementary Table 1).

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 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 (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 2B).

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 (Supplementary Table 2).

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 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) (Figure 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) (Supplementary 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 (Supplementary Table 4). 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).

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 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 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).

Subgroup analysis of TARE group

The Therasphere® group (n=45) and the SIR-Spheres® group (n=12) showed no significant differences in OS (2-year survival rates, 82.7% vs. 80.0%; P=0.4), TTP (cumulative 2-year progression rates, 51.5% vs. 43.1%; P=0.9), and TTIP (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 yttrium-90 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) (Supplementary 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 radiological and surgical treatments for HCC (Supplementary Table 6). TARE was 2.8-fold more expensive than surgical resection (USD 22,285

vs USD 8,082) in Korea. The TARE group showed significantly higher overall cost of treatment (mean, USD 53,541 vs. USD 16,393; P<0.001) and higher cost of additional treatment (mean, USD 596 vs. USD 292 per-patient-per-month; P=0.023) compared to the resection group (Supplementary Table 7).

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 yttrium-90 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 yttrium-90.(*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 surgical resection in a subgroup of patients with resectable single large HCC. Even though the TARE group was older (median, 69 vs. 60 years), 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 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.

In the present study, the TARE group underwent more additional treatments after the initial treatment than the resection group, however this difference was due to additional treatment performed because of the difficulty 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 two treatment groups.

When we further analyzed the cost of treatments, TARE was 2.8-fold more expensive than surgical resection in Korea (USD 22,285 vs USD 8,082). In addition, TARE was associated with more additional treatments and 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 a significantly higher overall cost of treatment than the surgical resection group (mean, USD 53,541 vs. USD 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 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 due to the future liver remnant and overall medical conditions. This is supported by the results of the present study, in which the TARE group had fewer adverse events and possibly more favorable post-treatment quality of life. However, given the retrospective nature of this study, 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, while 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 due to the difference in sensitivity of detecting nodules between CT and MRI. In spite of 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 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.

Our 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,(*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 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.(*44*) Third, owing to the operator-dependent nature of surgical resection and TARE, further studies are needed to assure the generalizability of the results of our study, which was conducted at 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,(*45*) 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. Our study focused

on TARE, a new modern radiotherapy with relatively high accessibility.(*46*)

CONCLUSION

In 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 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.

Disclosures

Jeong-Hoon Lee: Lecture fees from GreenCross Cell, Daewoong Pharmaceuticals and Gilead Korea; Yun Bin Lee: Research grant from Samjin Pharmaceuticals and Yuhan Pharmaceuticals; Yoon Jun Kim: Research grants from Bristol-Myers Squibb, Roche, JW Creagene, Bukwang Pharmaceuticals, Handok Pharmaceuticals, Hanmi Pharmaceuticals, Yuhan Pharmaceuticals and Pharmaking, and lecture fees from Bayer HealthCare Pharmaceuticals, Gilead Science, MSD Korea, Yuhan Pharmaceuticals, Samil Pharmaceuticals, CJ Pharmaceuticals, Bukwang Pharmaceuticals and Handok Pharmaceuticals; Jung-Hwan Yoon: Research grant from Bayer HealthCare Pharmaceuticals, Bukwang Pharmaceuticals and Daewoong Pharmaceuticals. All other authors have nothing to disclose.

Financial Support: The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

KEY POINTS

QUESTION: Is transarterial radioembolization (TARE) a potential alternative to surgical resection in patients with large single nodular hepatocellular carcinoma (HCC)?

PERTINENT FINDINGS: In this retrospective cohort study of newly diagnosed HCC patients with large single nodular tumor, TARE showed similar overall survival and time to progression with better safety profile compared to surgical resection.

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.

Graphical Abstract

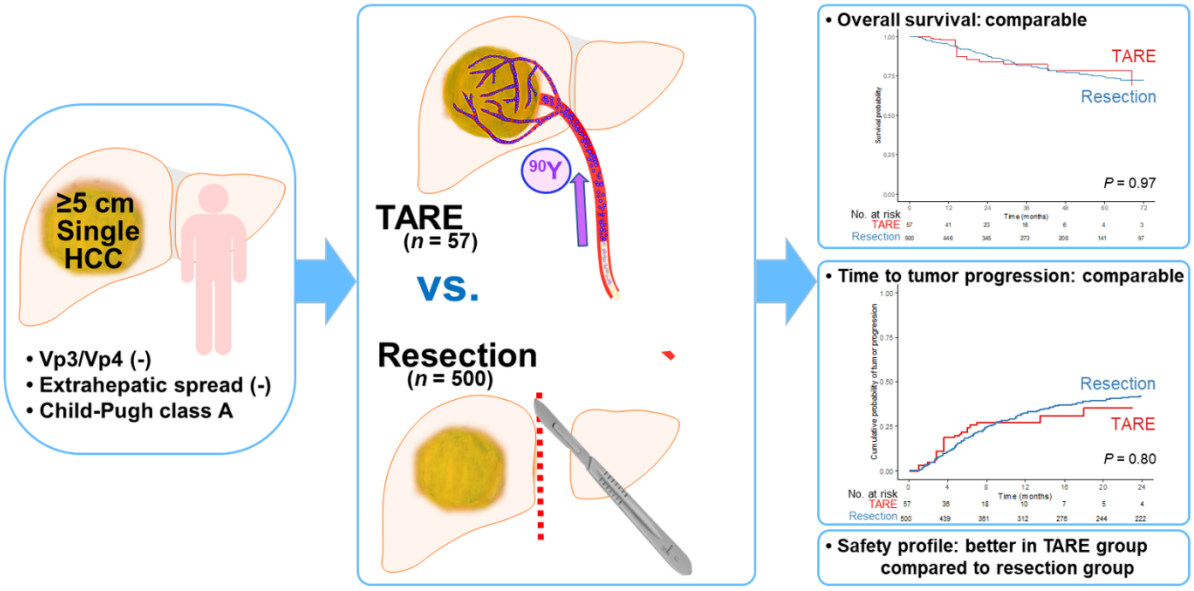

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TABLE 1. Baseline Characteristics of the Study Population

	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%)	
Male sex, N (%)	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, 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 (%)	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, 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%)	

*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.

TABLE 2. 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.

TABLE 3. Safety Assessment

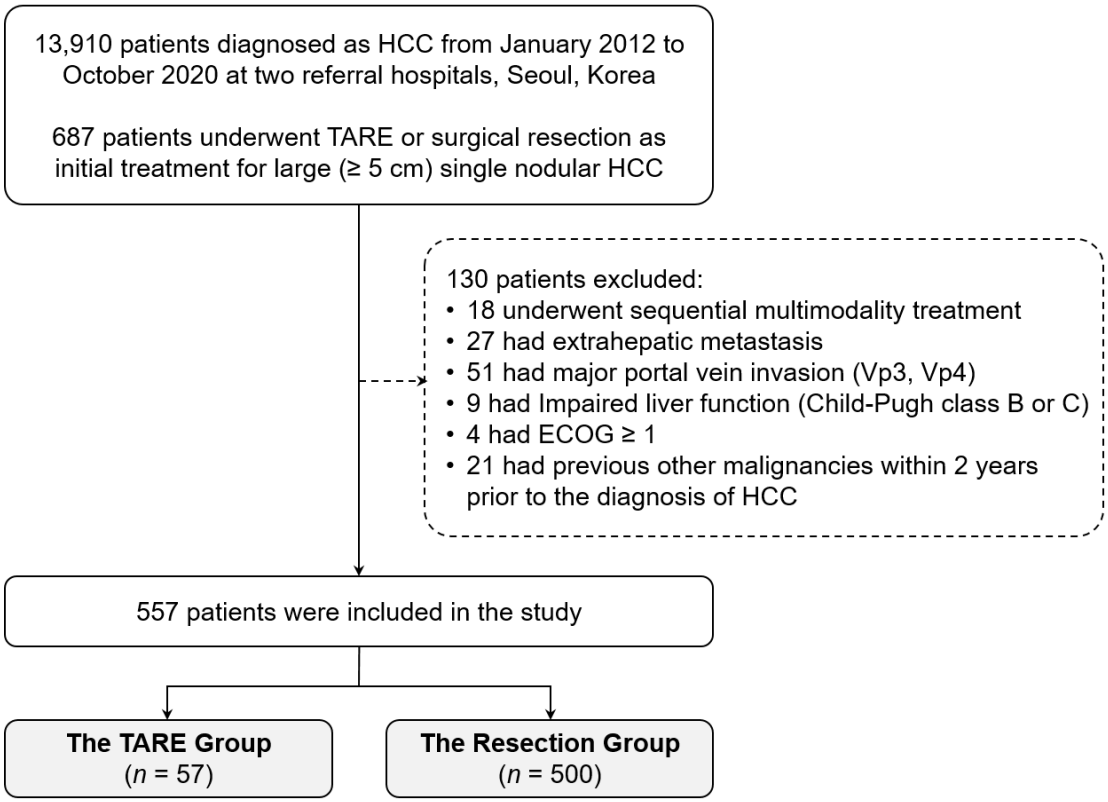
Adverse event	TARE (n=57)		Resection (n=500)		P value	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Overall incidence	25 (43.9%)	5 (8.8%)	500 (100%)	500 (100%)	<0.001	<0.001
Ascites	0	0	37 (7.4%)	5 (1.0%)	0.024	1.00
Fever	3 (5.3%)	0	104 (20.8%)	1 (0.2%)	0.008	1.00
Nausea	7 (12.3%)	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 (%).

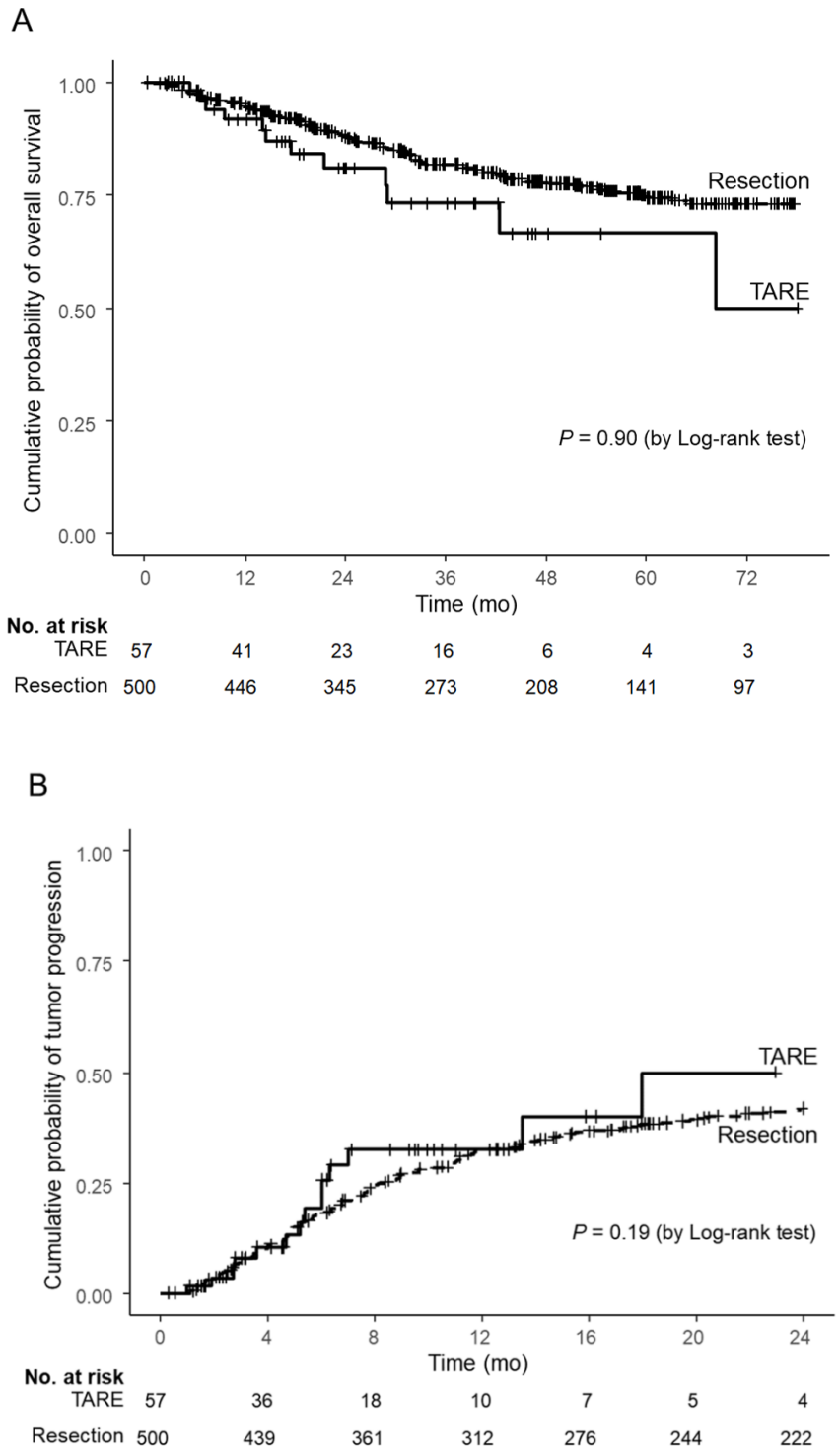
GI, gastrointestinal; AST, aspartate aminotransferase; ALT, alanine transaminase; PVT, portal vein thrombosis

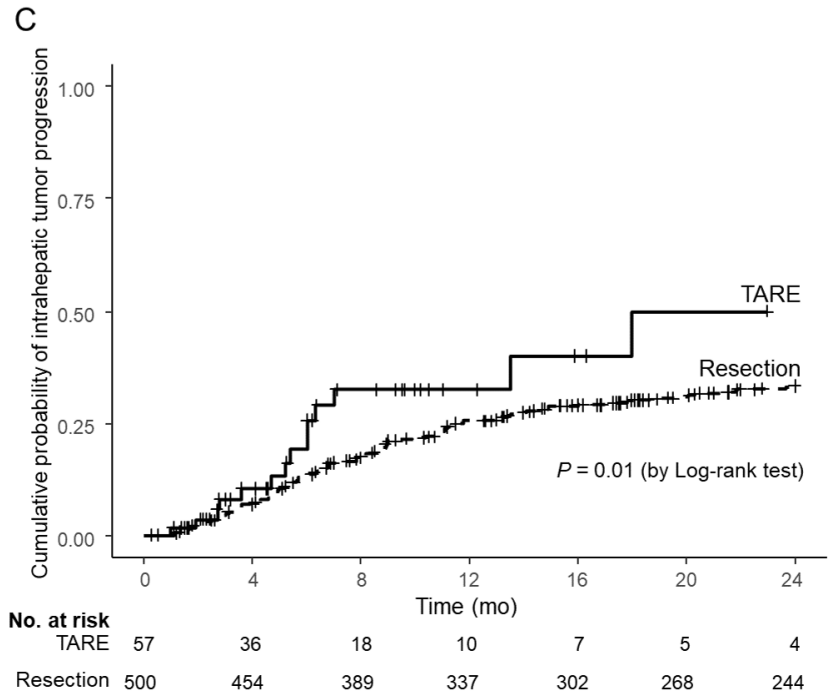
Figure 1. Flow chart of the study population



HCC, hepatocellular carcinoma; TARE, transarterial radioembolization; ECOG, Eastern Cooperative Oncology Group performance.

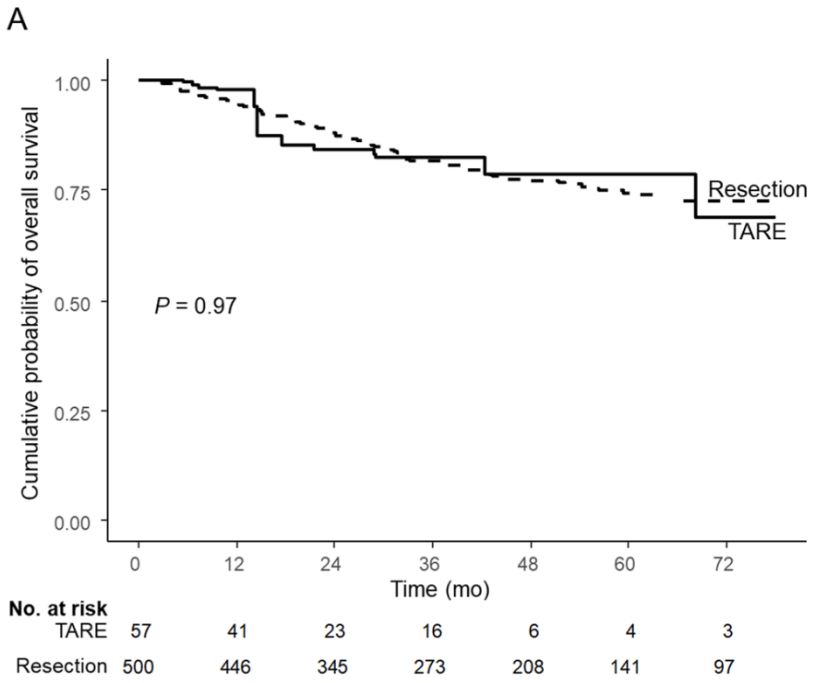
Figure 2. Cumulative probability of (A) overall survival, (B) tumor progression, and (C) intrahepatic tumor progression according to treatment groups (crude analysis)

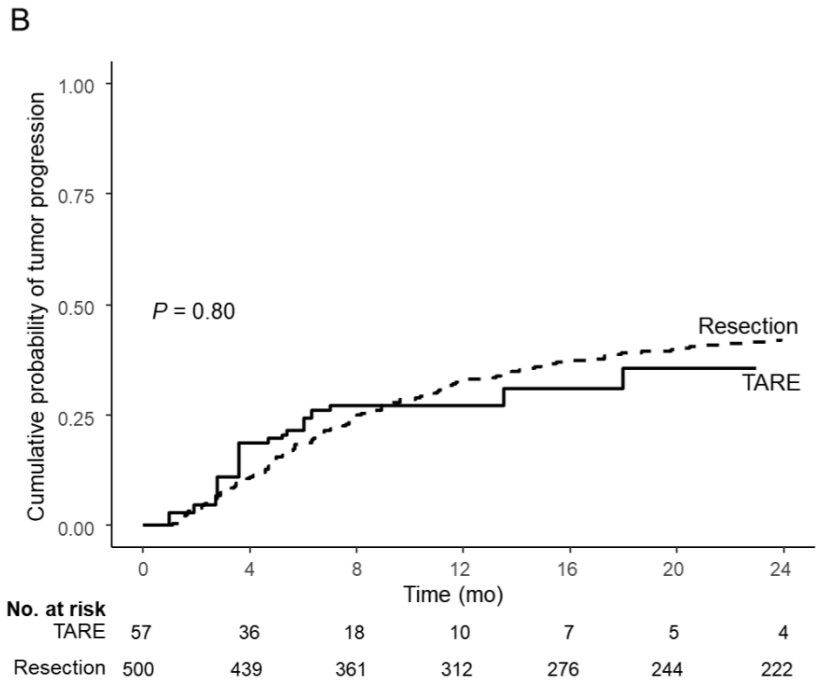


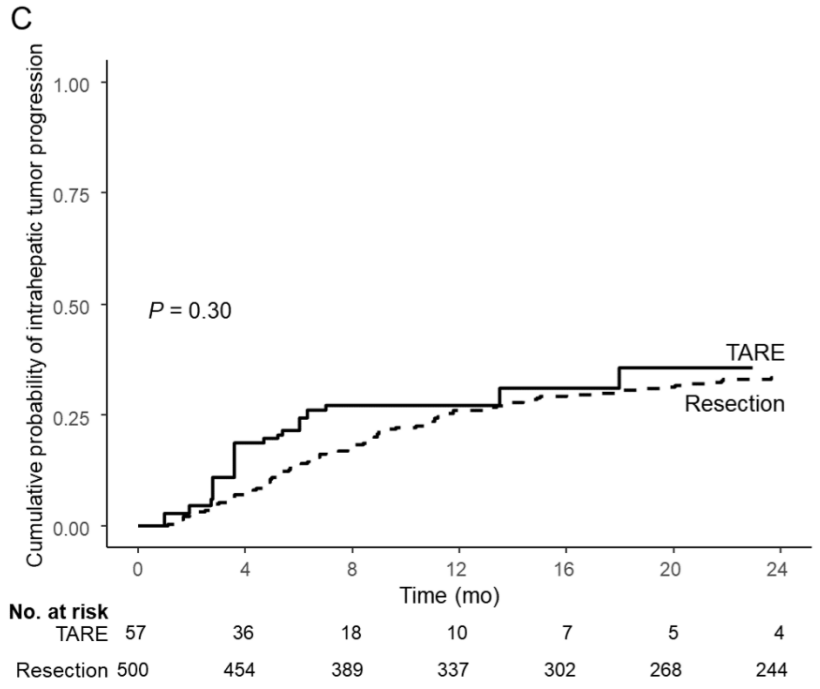


TARE, transarterial radioembolization

Figure 3. Cumulative probability of (A) overall survival, (B) tumor progression, and (C) intrahepatic tumor progression according to treatment groups (after employing inverse probability of treatment weighting)







TARE, transarterial radioembolization

Supplementary 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*)

Supplementary 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.

Supplementary 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.

Supplementary 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.

Supplementary 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

Supplementary 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

Supplementary 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

Supplementary 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