Comparison of Combined Transcatheter Arterial Chemoembolization and Radiofrequency Ablation with Surgical Resection by Using Propensity Score Matching in Patients with Hepatocellular Carcinoma within Milan Criteria[1]

Yoshitaka Takuma, MD
Hiroyuki Takabatake, MD
Youichi Morimoto, MD
Nobuyuki Toshikuni, MD
Takahisa Kayahara, MD
Yasuhiro Makino, MD
Hiroshi Yamamoto, MD

Purpose: To retrospectively compare the outcome of combined transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) (hereafter, TACE-RFA) with that of surgical resection (SR) in patients with hepatocellular carcinoma (HCC) within the Milan criteria.

Materials and Methods: Institutional review board approval and informed consent were obtained. From January 2000 to December 2010, 154 patients (mean age, 69.9 years; age range, 50–89 years; 107 men, 47 women) underwent TACE-RFA, and 176 patients (mean age, 66.9 years; age range, 29–83 years; 128 men, 48 women) underwent SR. Patients with HCC who underwent TACE-RFA or SR were enrolled if they met the following inclusion criteria: no previous HCC treatment, one HCC lesion no larger than 5 cm or up to three nodules smaller than 3 cm without vascular invasion or extrahepatic metastasis, and Child-Pugh class A or B disease. Cumulative overall survival (OS) and disease-free survival (DFS) rates were compared after adjustment with propensity score matching.

Results: After this adjustment, OS rates were comparable between the groups ($P = .393$), but DFS was superior in the SR group ($P < .048$). Among patients with very early stage HCC (lesions <2 cm in diameter), OS and DFS rates in the SR group were significantly higher than those in the TACE-RFA group ($P < .001$ and $P = .008$, respectively). However, adjustment with propensity score matching yielded comparable OS and DFS rates between the two groups ($P = .348$ and $P = .614$, respectively).

Conclusion: TACE-RFA may be a viable alternative treatment for early-stage HCC when SR is not feasible.

[1] From the Department of Gastroenterology, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710-8602, Japan (Y.T., H.T., Y. Morimoto, N.T., T.K., Y. Makino, H.Y.); and Department of Internal Medicine, National Hospital Organization Iwakuni Clinical Center, Yamaguchi, Japan (Y.T., Y. Makino). Received February 27, 2013; revision requested May 13; revision received July 24; accepted August 6; final version accepted August 14. **Address correspondence to** Y.T. (e-mail: *takuma@enjoy.ne.jp*).

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death globally (1). Patients who satisfy the Milan criteria (2) (one HCC ≤5 cm or as many as three nodules <3 cm without vascular invasion or extrahepatic metastasis) are optimal candidates for liver transplantation because of their early disease stage. Among these, patients with preserved liver function (Child-Pugh class A or B disease) may also qualify for curative treatments, such as surgical resection (SR) or local ablation, because these therapies confer lower risks and costs, circumvent the need for organ donors, and avoid the need for lifelong immunosuppression (3,4). Although SR is considered the main curative treatment for early-stage HCC, SR increases the risk of postoperative liver failure beyond that seen with local ablation therapies, such as percutaneous ethanol injection, radiofrequency ablation (RFA), and microwave ablation.

RFA is considered a viable alternative to SR in patients with early HCC, especially in patients with impaired liver function. Local tumor progression due to incomplete ablation is a negative prognostic factor in patients with HCC treated with RFA (5). Thus, to prolong survival, it is of paramount importance to reduce local tumor progression. The combined use of transcatheter arterial chemoembolization (TACE) and local ablative therapy may reduce local tumor progression arising from larger ablative lesions because of the synergistic effects induced by the decreased blood flow and minimized heat loss (6–8). However, although combined TACE and RFA (hereafter, TACE-RFA) improves local tumor control over that attained with only RFA in patients with early-stage HCC (9), the recurrence rate and risk factors for recurrence after TACE-RFA are not well established. The purpose of our study was to retrospectively compare the outcome of TACE-RFA with that of SR in patients with HCC within the Milan criteria.

Advances in Knowledge

- After adjustment with propensity score matching, the respective 1-, 3-, and 5-year overall survival (OS) rates were 99%, 88%, and 70% in the combined transcatheter arterial chemoembolization and radiofrequency ablation (TACE-RFA) group and 95%, 87%, and 75% in the surgical resection (SR) group; OS rates were comparable between the groups ($P = .393$).
- The respective 1-, 3-, and 5-year disease-free survival (DFS) rates were 85%, 35%, and 17% in the TACE-RFA group and 79%, 53%, and 32% in the SR group; DFS was superior in the SR group ($P < .048$).
- In patients with very early stage hepatocellular carcinoma (HCC) (lesions < 2 cm in diameter, adjustment with propensity score matching), the respective 1-, 3-, and 5-year OS rates were 100%, 90%, and 78% after TACE-RFA and 96%, 96%, and 83% after SR.
- In patients with very early stage HCC, the respective 1-, 3-, and 5-year DFS rates were 91%, 47%, and 40% after TACE-RFA and 89%, 68%, and 28% after SR.
- OS and DFS rates did not differ significantly between TACE-RFA and SR groups ($P = .348$ and $P = .614$, respectively).

Materials and Methods

Patients

In this retrospective cohort study, we reviewed the records of consecutive patients who underwent TACE-RFA or SR as the initial treatment for HCC in a database that was collected prospectively at two institutions (National Hospital Organization Iwakuni Clinial Center, Kurashiki Central Hospital) from January 2000 to December 2010. Informed consent was obtained from all patients for use of their clinical data. The institutional review board of each center approved this study. The diagnosis of HCC was corroborated by histologic findings or was made according to the American Association for the Study of Liver Diseases practice guidelines (10) by combining a diagnostic α-fetoprotein (AFP) level increase (>200 ng/mL [200 μg/L]) with a typical vascular pattern for HCC seen with one dynamic imaging technique or with a typical vascular pattern for HCC seen with two dynamic imaging techniques. The maximal diameter of the tumors was measured with axial computed tomography (CT) or magnetic resonance (MR) imaging.

Patients with initial treatment for HCC within the Milan criteria (2) and Child-Pugh class A or B cirrhosis were

Implications for Patient Care

- After we controlled for potential confounders, TACE-RFA conferred an OS benefit comparable with that of SR; however, the rate of DFS in the SR group appeared to be superior to that in the TACE-RFA group.
- TACE-RFA may be a viable alternative treatment modality for early-stage HCCs when SR is not feasible.

Published online before print
10.1148/radiol.13130387 **Content code:** IR

Radiology 2013; 269:927–937

Abbreviations:
AFP = α-fetoprotein
BCLC = Barcelona Clinic Liver Cancer
CI = confidence interval
DFS = disease-free survival
HCC = hepatocellular carcinoma
OS = overall survival
PIVKA-II = protein induced by vitamin K absence or antagonist-II
RFA = radiofrequency ablation
SI = Systéme International
SR = surgical resection
TACE = transcatheter arterial chemoembolization

Author contributions:
Guarantor of integrity of entire study, Y.T.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, Y.T.; clinical studies, all authors; statistical analysis, Y.T.; and manuscript editing, Y.T.

Conflicts of interest are listed at the end of this article.

See also the article by McDonald et al and the editorial by Levine and Kressel in this issue.

included. Patients with a performance status of 2 or greater (11), those with simultaneous malignancies, and those who were candidates for liver transplantation were excluded. In our study, 232 consecutive patients underwent SR, and 165 consecutive patients underwent TACE-RFA for initial treatment of HCC. Fifty-six patients in the SR group and 11 patients in the TACE-RFA group were excluded according to the exclusion criteria. Finally, 176 patients in the SR group and 154 patients in the TACE-RFA group were included in our study. The diagnosis of HCC was confirmed pathologically in all 176 patients (212 HCC nodules) in the SR group. In the TACE-RFA group, diagnosis was made at biopsy in 39 patients (41 HCC nodules) and at imaging, including CT during arterial portography and CT during hepatic arteriography, in 115 patients (190 HCC nodules).

Extrahepatic comorbidities included cardiovascular, renal, pulmonary, gastrointestinal, metabolic, hematologic, and neurologic diseases. In the TACE-RFA group, 44 patients (28.6%) had extrahepatic comorbidities (12 cardiovascular, 10 gastrointestinal, eight metabolic, six neurologic, four pulmonary, three hematologic, and one renal comorbidity). In the SR group, 33 patients (18.8%) had extrahepatic comorbidities (12 cardiovascular, eight neurologic, four metabolic, three gastrointestinal, three renal, two pulmonary, and one hematologic comorbidity).

Treatment

Senior hepatologists (Y.T, H.T., N.T., Y. Makino; 12–20 years of experience with interventional techniques) or radiologists (three nonauthors with 16–25 years of experience with interventional techniques) performed TACE by using the Seldinger technique of arterial embolization. A 4- or 3-F preshaped catheter (Terumo, Tokyo, Japan) was introduced via a punctured femoral artery. Superior mesenteric arterial portovenography and CT during arterial portography were performed to diagnose portal vein patency and localize HCC nodules. Celiac angiography and CT during hepatic arteriography were used to detect HCC nodules.

For tumor treatment, a 2- or 3-F microcatheter (Progreat Microcatheter System; Terumo) was superselectively placed in the feeding arteries of the tumor.

Chemolipiodolization was performed by using a mixture of 10–50 mg of epirubicin (Kyowa-Hakko, Tokyo, Japan) and 2–10 mL of lipiodol (Lipiodol Ultrafluid; Mitsui, Tokyo, Japan), which was slowly injected into the feeding arteries of the tumor. Thereafter, 1- to 2-mm gelatin sponge particles (Spongel, Yamanouchi, Tokyo, Japan; Gelpart, Nippon Kayaku, Tokyo, Japan) were delivered to the tumor until the flow was static. Within 2 weeks after TACE, RFA was performed percutaneously by senior hepatologists (Y.T, H.T., N.T., Y. Makino; 12–20 years of experience with interventional techniques). RFA was performed with ultrasonographic (US) guidance by using a commercially available system (Cool-Tip; Radionics, Burlington, Mass) with the patient under local anesthesia. One day after the first RFA session, treatment response was evaluated with dynamic CT, and technical success of RFA was defined as at least 0.5-cm hypoattenuation surrounding the entire tumor on both arterial and portal venous phase CT images. Additional RFA was performed until complete ablation of the tumor was achieved, if necessary.

An experienced surgical team (eight nonauthors, 12–30 years of experience with SR) anatomically resected the HCC, with an adequate nontumor margin. The indication for surgical resection and the surgical procedure were determined with a decision tree algorithm developed by Makuuchi et al (12) that accounted for tumor extent and hepatic functional reserve assessed with Child-Pugh classification and indocyanine green retention rate at 15 minutes. Briefly, trisegmentectomy and right hepatic lobectomy were considered possible when indocyanine green retention rate at 15 minutes was 0%–9%, left hepatic lobectomy and segmentectomy rates at 15 minutes were 10%–19%, subsegmentectomy rate at 15 minutes was 20%–29%, and partial resection rate at 15 minutes was 30%–39% (12). Anatomic resection was considered to include trisegmentectomy, lobectomy, segmentectomy, and subsegmentectomy. Other types of resection, such as partial resection, are classified as nonanatomic resection. If the patient's liver functional reserve permitted, anatomic resection was performed.

Major complications were defined as those that necessitated therapy with hospitalization, prolongation of the hospital stay, permanent adverse sequelae, or death. All other complications were considered minor.

Assessment and Follow-up

Patients were followed up at the outpatient clinic at 1- to 3-month intervals for measurement of serum AFP concentration and the protein induced by vitamin K absence or antagonist-II (PIVKA-II) concentration, and they were followed-up every 3 months with US, dynamic CT, or dynamic MR imaging. Intrahepatic tumor recurrence was confirmed with contrast material–enhanced CT, contrast-enhanced MR imaging, or angiography, and, if necessary, US-guided biopsy, by using the same criteria used to diagnose the primary HCC. Study endpoints included overall survival (OS) rate and disease-free survival (DFS) rate. Intrahepatic HCC recurrence was classified as recurrence either at a site distant from the primary tumor (distant intrahepatic recurrence) or adjacent to the treated site (local tumor progression).

The choice of treatment modalities for recurrent HCCs depended on patient preferences and the clinical practice of surgeons and hepatologists. In general, when recurrence was detected, the patients underwent SR, RFA, percutaneous ethanol injection, TACE, or systemic chemotherapy, or they received conservative care. The type of treatment depended on the site of the tumor, the liver function, and the general condition of the patient.

Statistical Analysis

The Mann-Whitney *U* test and the χ^2 test were used to analyze the differences in baseline demographic, clinical, and biochemical characteristics

Table 1

Demographic and Baseline Clinical Characteristics of Patients in the TACE-RFA and SR Groups

Variable	TACE-RFA Group (n = 154)	SR Group (n = 176)	P Value*
Sex			.516
Male	107 (69.5)	128 (72.7)	…
Female	47 (30.5)	48 (27.2)	…
Age (y)†	71.0 (65.0–75.5)	67.0 (61.3–73.0)	.002
Extrahepatic comorbidities			.035
Yes	44 (28.6)	33 (18.8)	…
No	110 (71.4)	143 (81.2)	…
ALT level (U/L)†‡	41.0 (28.5–68.0)	41.0 (25.3–72.5)	.809
Platelet count ($\times 10^4/\mu L$)†	9.5 (6.9–13.8)	13.1 (9.1–17.3)	<.001
Child-Pugh classification			<.001
Class A	114 (74.0)	169 (96.0)	…
Class B	40 (26.0)	7 (4.0)	…
Anti-HCV status			<.001
Positive	124 (80.5)	101 (57.4)	…
Negative	30 (19.5)	75 (42.6)	…
HBsAg			.001
Positive	8 (5.2)	30 (17.0)	…
Negative	146 (94.8)	146 (83.0)	…
AFP level§			.154
>20 ng/mL	83 (53.9)	81 (46.0)	…
≤20 ng/mL	71 (46.1)	95 (54.0)	…
PIVKA-II level			.315
>40 mAU/mL	79 (51.3)	100 (56.8)	…
≤40 mAU/mL	75 (45.7)	76 (43.2)	…
No. of nodules			<.001
Solitary	96 (62.3)	147 (83.5)	…
Multiple	58 (37.7)	29 (16.5)	…
Size of largest tumor (mm)†	20.0 (16.0–25.0)	25.0 (20.0–32.8)	<.001
Institution			.876
National Hospital Organization Iwakuni Clinical Center	52 (33.8)	58 (33.0)	…
Kurashiki Central Hospital	102 (66.2)	118 (67.0)	…

Note.—Unless otherwise indicated, data are number of patients and data in parentheses are percentages. ALT = alanine aminotransferase, Anti-HCV = antibody to hepatitis C virus, HBsAg = hepatitis B surface antigen.

* Mann-Whitney U test and χ^2 test were used to analyze the differences in background and biochemical data between the two groups.

† Data are medians, and data in parentheses are the interquartile range.

‡ To convert to Systéme International (SI) units (microkatal per liter), multiply by 0.0167.

§ To convert to SI units (micrograms per liter), multiply by 1.0.

between TACE-RFA and SR groups. OS and DFS rates were analyzed with the Kaplan-Meier method. Intergroup differences were compared with the log-rank test. Factors potentially influencing OS and DFS were analyzed with a Cox proportional hazards regression model, which included 14 variables (treatment type [TACE-RFA or SR], sex, age, extrahepatic comorbidities, alanine aminotransferase level, platelet count, Child-Pugh classification, antibody to hepatitis C virus status, hepatitis B surface antigen status, AFP level, PIVKA-II level, tumor number, tumor size, and institution). All variables in the univariate analyses were entered into the multivariate analysis to assess their significance as independent predictors. Hazard ratios and respective 95% confidence intervals were compared.

To minimize the effect of potential confounders on selection bias, propensity scores were generated by using binary logistic regression to estimate the probability that a patient would undergo SR instead of TACE-RFA. Independent variables entered into the propensity model included sex, age, extrahepatic comorbidities, alanine aminotransferase level, platelet count, Child-Pugh classification, antibody to hepatitis C virus status, hepatitis B surface antigen status, AFP level, PIVKA-II level, tumor number, tumor size, and institution. One-to-one matching between the groups was accomplished by using the nearest-neighbor matching method (13,14). Briefly, distribution of propensity scores was evaluated by treatment group to examine for sufficient overlap among the groups to ensure comparability. We trimmed the sample by removing 180 patients (TACE-RFA, n = 79; SR, n = 101) from the 330 patients with nonoverlapped propensity score distribution. Thus, adjusted comparisons by propensity scores were based on data from 75 patients per treatment arm. After adjustment for these factors, OS and DFS rates were recalculated for the two groups. Statistical analyses were performed by using statistical software (SPSS, version 16.0 for Windows; SPSS, Chicago, Ill). Statistical tests were two sided. $P < .05$ indicated a significant difference.

Results

Baseline Characteristics of TACE-RFA and SR Groups

Table 1 shows the patient characteristics for the two groups. Patients who underwent TACE-RFA were significantly older (P = .002), were more frequently classified as having Child-Pugh class B disease ($P < .001$), had a higher rate of extrahepatic comorbidities (P = .035), and had higher antibody to hepatitis C virus positivity ($P < .001$) than did patients who underwent SR. In contrast, patients who underwent SR had larger tumors ($P < .001$) and more frequently had a single nodule ($P < .001$), higher platelet counts ($P < .001$), and a higher rate of hepatitis B surface antigen positivity (P = .001)

than did patients who underwent TACE-RFA. In the TACE-RFA group, 184 HCC nodules were diagnosed with dynamic CT or MR imaging, and the remaining six HCC nodules were detected with combined use of CT during both arterial portography and hepatic arteriography. Finally, 190 HCC nodules were accurately diagnosed with imaging findings after TACE. Lipiodol uptake was observed in all 231 HCC nodules, and all nodules were ablated.

Technical Success of TACE-RFA

Technical success was achieved in all 154 patients. One RFA session was performed in 125 (81.2%) patients, two RFA sessions were performed in 23 (14.9%) patients, and three RFA sessions were performed in six (3.9%) patients.

Technical Success of SR

In the SR group, anatomic resection was performed in 69 patients (39.2%) (trisegmentectomy [n = 3], lobectomy [n = 13], segmentectomy [n = 20], and subsegmentectomy [n = 33]). In the remaining 107 patients (60.8%), nonanatomic resection was performed.

OS Rate

The median observation period was 46 months (interquartile range, 30–73 months) for all patients, 45 months (interquartile range, 28–61 months) for patients who underwent TACE-RFA, and 52 months (interquartile range, 34–84 months) for patients who underwent SR. Among the 154 patients who underwent TACE-RFA, 91 were alive, 60 had died, and three were lost to follow-up by the end of the study. Among the 176 patients who underwent SR, 112 were alive, 59 had died, and five were lost to follow-up. The respective 1-, 3-, and 5-year OS rates were 99% (95% confidence interval [CI]: 95%, 100%), 83% (95% CI: 75%, 88%), and 58% (95% CI: 47%, 67%) in the TACE-RFA group and 97% (95% CI: 92%, 98%), 87% (95% CI: 80%, 91%), and 74% (95% CI: 66%, 81%) in the SR group. OS rates in the SR group significantly exceeded those in the TACE-RFA group (P = .003) (Fig 1, *A*). In all patients, TACE-RFA (P = .003), lower platelet counts ($\leq 10^5/\mu L$) (P = .002), Child-Pugh class B disease ($P < .001$), antibody to hepatitis C virus positivity (P = .006), hepatitis B surface antigen negativity (P = .020), higher AFP levels (>20 ng/mL [>20 μg/L]) (P = .002), and higher PIVKA-II levels (>40 mAU/mL) (P = .001) were significantly associated with poor OS in univariate analyses (Table 2). In multivariate analyses, higher AFP levels (>20 ng/mL [>20 μg/L]) (P = .039) and higher PIVKA-II levels (>40 mAU/mL) (P = .012) were independent predictors of poor OS. However, treatment with TACE-RFA as opposed to treatment with SR was not an independent risk factor for poor OS (P = .127) (Table 2).

DFS Rate

A total of 96 (62.3%) HCCs in the TACE-RFA group and 93 (52.8%) HCCs in the SR group recurred. Ninety-five recurrences after TACE-RFA were intrahepatic recurrences (85 distant intrahepatic, 10 local tumor progressions), and one involved an extrahepatic recurrence (lymph node metastasis). Ninety-one recurrences in patients who underwent SR were intrahepatic recurrences (89 distant intrahepatic recurrences, two local tumor progressions), and two involved extrahepatic (bone and lung) metastases. Local tumor progressions occurred significantly more frequently with TACE-RFA than with SR (6.5% vs 1.1%, P = .010). The respective 1-, 3-, and 5-year DFS rates were 85% (95% CI: 79%, 90%), 37% (95% CI, 29%, 45%), and 15% (95% CI: 9%, 23%) in the TACE-RFA group and 84% (95% CI: 78%, 89%), 56% (95% CI: 48%, 63%), and 40% (95% CI: 32%, 48%) in the SR group. The DFS rate in the SR group was significantly higher than that in the TACE-RFA group ($P < .001$) (Fig 1, *B*). Among all patients, TACE-RFA ($P < .001$), lower platelet count ($P < .001$), antibody to hepatitis C virus positivity (P = .002), hepatitis B surface antigen negativity (P = .005), higher PIVKA-II level (P = .018), multinodularity ($P < .001$), and larger tumor size (>20 mm) (P = .024) were significantly associated with tumor recurrence in univariate analyses (Table 3). In multivariate analysis, TACE-RFA (P = .013), lower platelet count (P = .003), higher PIVKA-II level (P = .031), multinodularity ($P < .001$), and larger tumor size (P = .019) were independent risk factors associated with tumor recurrence (Table 3).

Comparison of OS and DFS Rates between TACE-RFA and SR Groups after One-To-One Propensity Score Matching

A total of 75 patients from each group were matched by applying one-to-one propensity score matching. Confounding factors were well-matched between the two groups (Table 4). The respective 1-, 3-, and 5-year OS rates were 99% (95% CI: 91%, 100%), 88% (95% CI: 77%, 94%), and 70% (95% CI: 55%, 81%) in the TACE-RFA group and 95% (95% CI: 86%, 98%), 87% (95% CI: 76%, 93%), and 75% (95% CI: 62%, 84%) in the SR group. OS rates between the two groups did not differ significantly (P = .393) (Fig 1, *C*). The respective 1-, 3-, and 5-year DFS rates were 85% (95% CI: 74%, 91%), 35% (95% CI: 23%, 46%), and 17% (95% CI: 8%, 29%) in the TACE-RFA group and 79% (95% CI: 68%, 87%), 53% (95% CI: 40%, 64%), and 32% (95% CI: 20%, 44%) in the SR group. The DFS rate in the SR group significantly exceeded that in the TACE-RFA group (P = .048, log-rank test) (Fig 1, *D*).

Comparison of OS and DFS Rates in TACE-RFA and SR Groups with Very Early Stage HCC

Among the 330 study subjects, 59 patients who underwent TACE-RFA and 52 who underwent SR were classified as having Barcelona Clinic Liver Cancer (BCLC) very early stage HCC (solitary HCC <2 cm) and were further analyzed (10). In comparison with patients who underwent SR, those who underwent TACE-RFA were significantly older (P = .001), were more frequently classified as having Child-Pugh class B disease ($P < .001$), and had lower platelet counts ($P < .001$), a higher rate of antibody to hepatitis C virus positivity (P = .048), a lower rate of hepatitis B surface antigen positivity (P = .035), and higher

Figure 1

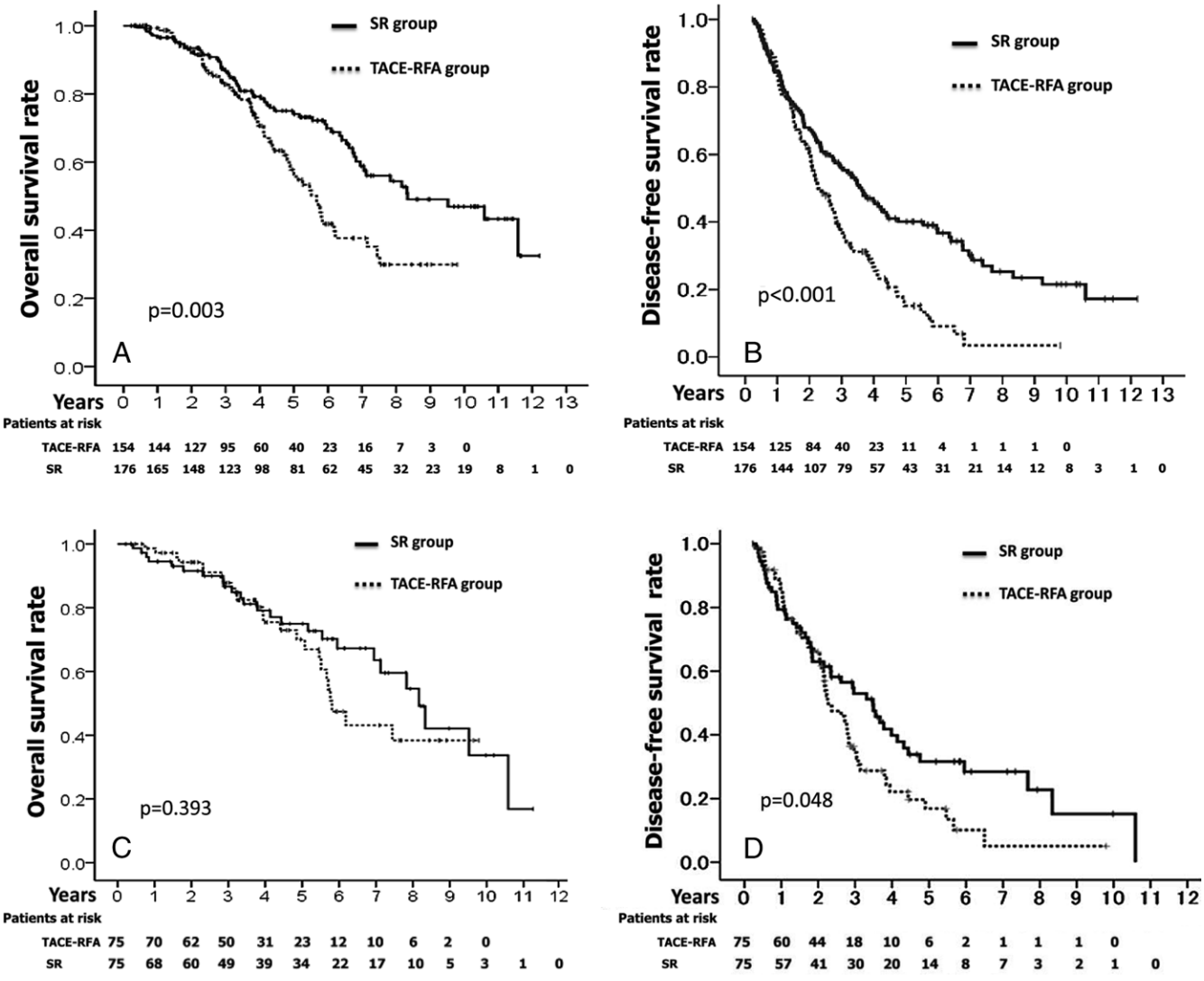

Figure 1: Survival curves in patients with HCC within Milan criteria who underwent SR and TACE-RFA. *A,* Cumulative OS curves in patients with HCC who underwent SR and TACE-RFA. *B,* Cumulative DFS curves in patients with HCC who underwent SR and TACE-RFA. *C,* Cumulative OS curves after propensity score matching in patients with HCC who underwent SR and TACE-RFA. *D,* Cumulative DFS curves after propensity score matching in patients with HCC who underwent SR and TACE-RFA.

PIVKA-II levels (P = .049) (Table 5). The respective 1-, 3-, and 5-year OS rates were 100%, 83% (95% CI: 71%, 91%), and 58% (95% CI: 41%, 72%) in the TACE-RFA group and 98% (95% CI: 87%, 100%), 96% (95% CI: 84%, 99%), and 89% (95% CI: 75%, 95%) in the SR group. The OS rate after SR was significantly higher than that after TACE-RFA ($P < .001$) (Fig 2, *A*). The recurrence rates for BCLC very early stage HCCs were 42% (n = 25) in the TACE-RFA group and 50% (n = 26) in the SR group. No extrahepatic recurrences occurred in either group. Local tumor progression occurred in one patient (2%) after TACE-RFA and in one patient (2%) after SR, resulting in similar frequencies of local tumor progression (P = .928). The respective 1-, 3-, and 5-year DFS rates were 93% (95% CI: 83%, 97%), 54% (95% CI: 39%, 66%), and 24%(95% CI: 12%, 39%) after TACE-RFA and 94% (95% CI: 83%, 98%), 72% (95% CI: 57%, 82%), and 52% (95% CI: 37%, 66%) after SR. The DFS rate of the SR group significantly exceeded that of the TACE-RFA group (P = .008) (Fig 2, *B*). Among the 75 patients in each group in which we applied one-to-one propensity score matching, 24 patients who underwent TACE-RFA and 27 patients who

Table 2

Risk of Death in Patients with HCC after Curative Therapy

Variable	No. of Cases	Univariate Analysis		Multivariate Analysis	
		Hazard Ratio	*P* Value*	Hazard Ratio	*P* Value*
Modality (TACE-RFA vs SR)	176/154	1.756 (1.213, 2.541)	.003	1.403 (0.908, 2.165)	.127
Sex (male vs female)	235/95	0.921 (0.607, 1.397)	.699	1.104 (0.701, 1.736)	.770
Age (>70 y vs ≤70 y)	148/182	1.344 (0.926, 1.951)	.120	1.118 (0.733, 1.706)	.605
Extrahepatic comorbidities (yes vs no)	77/253	0.942 (0.622, 1.426)	.778	0.894 (0.574, 1.392)	.621
ALT level (>80 IU/L vs ≤80 IU/L)†	64/266	0.953 (0.613, 1.482)	.831	0.908 (0.560, 1.473)	.697
Platelet count (≤10^5/μL vs >10^5/μL)	140/190	1.749 (1.218, 2.512)	.002	1.464 (0.991, 2.165)	.055
Child-Pugh classification (B vs A)	47/283	2.354 (1.486, 3.730)	<.001	1.660 (0.996, 2.768)	.052
Anti-HCV (positivity vs negativity)	225/105	1.877 (1.194, 2.951)	.006	1.405 (0.810, 2.437)	.226
HBsAg (positivity vs negativity)	38/292	0.425 (0.206, 0.876)	.020	0.703 (0.296, 1.672)	.425
AFP level (>20 ng/mL vs ≤20 ng/mL)‡	164/166	1.760 (1.221, 2.537)	.002	1.535 (1.022, 2.306)	.039
PIVKA-II level (>40 mAU/mL vs ≤40 mAU/mL)	179/151	1.848 (1.275, 2.680)	.001	1.670 (1.121, 2.489)	.012
No. of nodules (multiple vs solitary)	87/243	1.340 (0.885, 2.031)	.167	1.329 (0.851, 2.076)	.210
Size of largest tumor (>20 mm vs ≤20 mm)	184/146	1.386 (0.962, 1.997)	.080	1.417 (0.957, 2.097)	.082
Institution (National Hospital Organization Iwakuni Clinical Center vs Kurashiki Central Hospital)	110/220	0.725 (0.486, 1.082)	.115	0.876 (0.572, 1.342)	.542

Note.—Data in parentheses are 95% CIs. ALT = alanine aminotransferase, Anti-HCV = antibody to hepatitis C virus, HBsAg = hepatitis B surface antigen.

* *P* values were determined with Cox proportional hazards regression models. *P* < .05 indicated a significant difference.

† To convert to SI units (microkatal per liter), multiply by 0.0167.

‡ To convert to SI units (micrograms per liter), multiply by 1.0.

Table 3

Risk of Tumor Recurrence in Patients with HCC after Curative Therapy

Variable	No. of Cases	Univariate Analysis		Multivariate Analysis	
		Hazard Ratio	*P* Value*	Hazard Ratio	*P* Value*
Modality (TACE-RFA vs SR)	176/154	1.736 (1.318, 2.287)	<.001	1.511 (1.089, 2.092)	.013
Sex (male vs female)	235/95	1.051 (0.777, 1.423)	.746	1.165 (0.837, 1.621)	.365
Age (>70 years vs ≤70 years)	148/182	1.109 (0.845, 1.456)	.456	0.920 (0.675, 1.254)	.597
Extrahepatic comorbidities (yes vs no)	77/253	0.928 (0.686, 1.257)	.630	0.803 (0.582, 1.107)	.180
ALT level (>80 IU/L vs ≤80 IU/L)†	64/266	1.286 (0.939, 1.761)	.117	1.150 (0.815, 1.623)	.427
Platelet count (≤10^5/μL vs >10^5/μL)	140/190	1.690 (1.292, 2.210)	<.001	1.555 (1.157, 2.088)	.003
Child-Pugh classification (B vs A)	47/283	1.213 (0.832, 1.766)	.32	0.802 (0.529, 1.215)	.298
Anti-HCV (positivity vs negativity)	225/105	1.626 (1.192, 2.218)	.002	1.164 (0.790, 1.715)	.443
HBsAg (positivity vs negativity)	38/292	0.514 (0.323, 0.819)	.005	0.636 (0.358, 1.132)	.124
AFP level (>20 ng/mL vs ≤20 ng/mL)‡	164/166	1.296 (0.993, 1.691)	.057	1.269 (0.933, 1.725)	.129
PIVKA-II level (>40 mAU/mL vs ≤40 mAU/mL)	179/151	1.383 (1.058, 1.809)	.018	1.368 (1.030, 1.816)	.031
No. of nodules (multiple vs solitary)	87/243	2.378 (1.767, 3.199)	<.001	2.368 (1.727, 3.246)	<.001
Size of largest tumor (>20 mm vs ≤20 mm)	184/146	1.365 (1.042, 1.787)	.024	1.416 (1.060, 1.892)	.019
Institution (National Hospital Organization Iwakuni Clinical Center vs Kurashiki Central Hospital)	110/220	0.756 (0.567, 1.008)	.056	0.859 (0.638, 1.156)	.315

Note.—Data in parentheses are 95% CIs. ALT = alanine aminotransferase, Anti-HCV = antibody to hepatitis C virus, HBsAg = hepatitis B surface antigen.

* *P* values were determined with Cox proportional hazards regression models. *P* < .05 indicated a significant difference.

† To convert to SI units (microkatal per liter), multiply by 0.0167.

‡ To convert to SI units (micrograms per liter), multiply by 1.0.

underwent SR were classified as having BCLC very early stage HCC and were analyzed further. The respective OS rates at 1, 3, and 5 years were 100%, 90% (95% CI: 66%, 97%), and 78% (95% CI: 51%, 91%) after TACE-RFA and 96% (95% CI: 76%, 99%), 96% (95% CI: 76%, 99%), and 83% (95% CI: 60%, 93%) after SR. The respective

Table 4

Demographic and Baseline Characteristics of TACE-RFA and SR Groups by Propensity Analysis with One-to-One Nearest-Neighbor Matching Method

Variable	TACE-RFA Group ($n = 75$)	SR Group ($n = 75$)	*P* Value*
Sex			.157
Male	56 (75)	48 (64)	…
Female	19 (25)	27 (46)	…
Age (y)†	70.0 (60.8–76.0)	70.0 (64.0–74.0)	.461
ALT level (IU/L)†‡	49.0 (26.8–74.3)	40.0 (26.0–70.0)	.373
Extrahepatic comorbidities			.185
Yes	22 (29)	15 (20)	…
No	53 (71)	60 (80)	…
Platelet count ($\times 10^4/\mu L$)†	11.6 (8.1–14.9)	11.8 (8.6–14.7)	.619
Child-Pugh classification			.513
Class A	71 (95)	69 (92)	…
Class B	4 (5)	6 (8)	…
Anti-HCV			.675
Positivity	62 (83)	60 (80)	…
Negativity	13 (17)	15 (20)	…
HBsAg			.731
Positivity	4 (5)	5 (7)	…
Negativity	71 (95)	70 (93)	…
AFP level§			.414
>20 ng/mL	36 (48)	41 (55)	…
≤20 ng/mL	39 (52)	34 (45)	…
PIVKA-II level			.744
>40 mAU/mL	38 (51)	40 (53)	…
≤40 mAU/mL	37 (49)	35 (47)	…
No. of nodules			.712
Solitary	54 (72)	56 (75)	…
Multiple	21 (28)	19 (25)	…
Size of largest tumor (mm)†	22.0 (18.0–27.0)	23.0 (18.0–30.0)	.385
Institution			.170
National Hospital Organization Iwakuni Clinical Center	22 (29)	30 (40)	…
Kurashiki Central Hospital	53 (71)	45 (60)	…

Note.—Unless otherwise indicated, data in parentheses are 95% CIs. ALT = alanine aminotransferase, Anti-HCV = antibody to hepatitis C virus, HBsAg = hepatitis B surface antigen.

* Mann-Whitney *U* test and χ^2 test were used to analyze the differences in background and biochemical data between the two groups.

† Data are medians and data in parentheses are interquartile range.

‡ To convert to SI units (microkatal per liter), multiply by 0.0167.

§ To convert to SI units (micrograms per liter), multiply by 1.0.

1-, 3-, and 5-year DFS rates were 91% (95% CI: 69%, 98%), 47% (95% CI: 24%, 67%), and 40% (95% CI: 18%, 61%) after TACE-RFA and 89% (95% CI: 69%, 96%), 68% (95% CI: 46%, 83%), and 28% (95% CI: 11%, 48%) after SR. OS and the DFS rates did not differ significantly between groups ($P = .348$ and $P = .614$, respectively) (Fig 2, *C* and *D*).

Complications

One major complication (pneumothorax) occurred in one (0.6%) patient after TACE-RFA. This patient recovered after conservative treatment. No treatment-related deaths occurred in the TACE-RFA group. Two major complications (liver failure and sepsis) occurred in two (1.1%) patients after SR, but these patients recovered. No death was considered related to surgery. In the TACE-RFA group, three (1.9%) minor complications were observed. Minor burns occurred in two patients, and a pleural effusion was observed in one patient. In the SR group, no minor complications were observed.

Discussion

Previous studies have cited local tumor progression rates after TACE-RFA as high as 2.9%–14.5% over median follow-up periods ranging from 37 to 50 months (9,15,16). As in prior studies, local progression in our study occurred in 10 (6.5%) of 154 patients during a median follow-up period of 45 months. In comparison, local tumor progression rates after RFA alone have generally exceeded those of TACE-RFA, with previously published rates as high as 15.2%–41% over median follow-up periods ranging from 16 to 38 months (9,17,18). In Kim et al (9), TACE-RFA improved tumor control over that achieved with RFA alone in the treatment of small HCCs. In a recent randomized controlled study, TACE-RFA was superior to RFA alone in improving OS and DFS in patients with HCCs smaller than 7 cm (19).

TACE-RFA may improve local tumor control via several mechanisms. First, an enlarged ablative zone reduces heat loss, and elimination of blood flow by TACE improves coverage of undetected micrometastasis around the main tumor. This is beneficial because recurrent tumors commonly occur in the remnant liver near the surgical region (20). Second, TACE alone is also effective in treating undetected micrometastasis adjacent to the main tumor. Thus, combining TACE and RFA is expected to reduce local progression and improve both OS and DFS rates in patients with small- or medium-sized HCCs (6,19,21).

Furthermore, some retrospective studies have suggested that TACE-RFA may yield OS rates comparable with those of SR (15,16). Yamakado et al (15) reported that patients with early-stage HCC who underwent TACE-RFA had OS and DFS rates similar to those in patients who underwent SR. In contrast, Kagawa et al (16) reported that when compared

with SR, TACE-RFA in patients with early-stage HCC yielded a similar rate of OS but a lower rate of DFS. In our study, the OS and DFS rates after TACE-RFA in patients with early stage HCCs within the Milan criteria were significantly lower than those observed after SR. These findings may be explained by differences in baseline patient characteristics (ie, the TACE-RFA group was significantly older and had higher frequencies of HCV and multinodularity, a lower prevalence of HBV, and poorer liver functional reserve when compared with the SR group). Older patients and those with poor liver functional reserve might elect to undergo RFA, which is a less invasive modality, because these patients more commonly have extrahepatic comorbidities. Furthermore, compared with HBV infection, HCV infection is associated with a higher tumor recurrence rate after hepatic resection in patients with small HCCs (22,23). These patients tend to undergo RFA instead of SR because of preference, extrahepatic comorbidities, and poor liver functional reserve. However, after adjustment by propensity score matching, patients who underwent TACE-RFA had a similar OS rate but had poorer DFS when compared with patients who underwent SR. Our findings are similar to those reported by Kagawa et al (16).The difference between DFS rates may be mainly due to local tumor progressions, as reflected in the higher frequency of local tumor progressions after TACE-RFA versus SR. Although higher serum AFP and PIVKA-II levels were associated with poorer OS in the multivariate analyses, TACE-RFA was not associated with poorer OS. However, TACE-RFA was associated with a higher incidence of tumor recurrence at multivariate analysis.

Published 5-year OS and DFS rates in patients with solitary HCCs measuring no larger than 2 cm (BCLC very early stage disease) have ranged from 62.1% to 91.5% (24–26) and from 40.7% to 51.3% (24,25), respectively, after SR and from 71.9% to 77.8% (24–26) and from 29.3% to 59.8% (24,25), respectively, after RFA.

Thus, RFA may be considered the treatment of choice in patients with solitary HCC measuring no larger than 2 cm even when SR is possible (27). In our study, SR improved OS and DFS rates compared with those attained with TACE-RFA in patients with BCLC very early stage HCCs. However, after adjustment by propensity score matching, OS and DFS rates after SR were comparable with those after TACE-RFA and SR. These inconsistent findings may be mainly due to differences in patient characteristics rather than local tumor progressions because the frequencies of local tumor progressions in the two groups were rare and similar. Thus, after propensity score matching, local tumor progressions did not affect DFS rates in patients with very early stage HCC, unlike in patients with early stage HCC.

In our study, both treatment groups had low rates of major complications, and there were no treatment-related deaths. The rate of major complications related to SR in our study was 1.1%, which was comparable with that in other studies (range, 0%–3.2%) (15,28). A few reports have shown TACE-RFA to be safe, with

Table 5

Demographic and Baseline Clinical Characteristics of Patients Who Underwent TACE-RFA versus Those Who Underwent SR for BCLC Very Early Stage HCC

Variable	TACE-RFA Group ($n = 59$)	SR Group ($n = 52$)	*P* Value*
Sex		34/18 (65.4)	.914
Male	38 (64)	34 (65)	…
Female	21 (46)	18 (35)	…
Age (y)†	72.0 (65.0–75.3)	66.0 (59.0–71.0)	.001
Extrahepatic comorbidities			.240
Yes	17 (29)	10 (19)	…
No	42 (71)	42 (81)	…
ALT (IU/L)†‡	34.5 (24.0–60.5)	46.5 (30.0–82.0)	.050
Platelet count ($\times 10^4/\mu L$)†	9.1 (6.2–12.0)	12.5 (8.5–14.7)	<.001
Child-Pugh classification			<.001
Class A	39 (66)	52 (100)	…
Class B	20 (34)	0	…
Anti-HCV			.048
Positivity	49 (83)	38 (65)	…
Negativity	10 (17)	18 (35)	…
HBsAg			.035
Positivity	3 (5)	10 (19)	…
Negativity	56 (95)	42 (81)	…
AFP level§			.172
(>20 ng/mL	36 (61)	25 (48)	…
≤20 ng/mL	23 (39)	27 (52)	…
PIVKA-II level	29/30 (49.2)	16/36 (30.8)	.049
>40 mAU/mL	29 (49)	16 (31)	…
≤40 mAU/mL	30 (51)	36 (69)	…
Size of largest tumor (mm)†	16.0 (14.8–19.3)	17.0 (15.0–19.8)	.458
Institution			.379
National Hospital Organization Iwakuni Clinical Center	18 (31)	12 (23)	…
Kurashiki Central Hospital	41 (69)	40 (77)	…

Note.—Unless otherwise indicated, data in parentheses are 95% CIs. ALT = alanine aminotransferase, Anti-HCV = antibody to hepatitis C virus, HBsAg = hepatitis B surface antigen.

* Mann-Whitney *U* test and χ^2 test were used to analyze the differences in background and biochemical data between the two groups.

† Data are medians and data in parentheses are interquartile range.

‡ To convert to SI units (microkatal per liter), multiply by 0.0167.

§ To convert to SI units (micrograms per liter), multiply by 1.0.

Figure 2

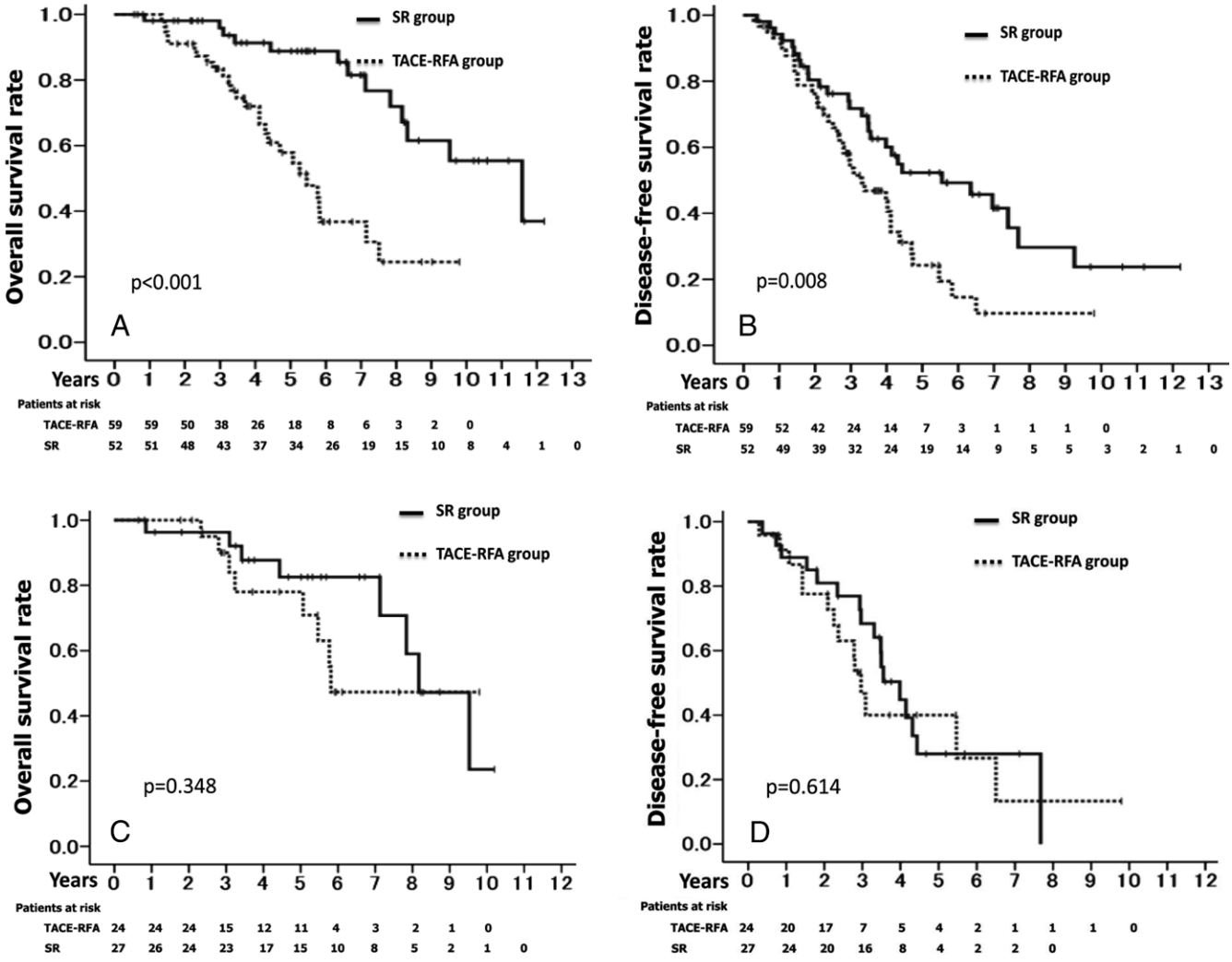

Figure 2: Survival curves in patients with BCLC very early stage HCC who underwent SR and TACE-RFA. *A,* Cumulative OS curves in patients with HCC who underwent SR and TACE-RFA. *B,* Cumulative DFS curves in patients with HCC who underwent SR and TACE-RFA. *C,* Cumulative OS curves after propensity score matching in patients with HCC who underwent SR and TACE-RFA. *D,* Cumulative DFS curves after propensity score matching in patients with HCC who underwent SR and TACE-RFA.

low rates of major complications (range, 0%–2.2%) (15,16), and the rate of major complications related to TACE-RFA in our study was 0.6%. Our results are similar to those in previous studies, and our results show that TACE-RFA is safe.

Our study included unmatched characteristics between the two groups because of its nonrandomized design; thus, the two groups differed significantly in many variables. Although a well-designed randomized comparative trial of TACE-RFA and SR may help resolve this issue, it is difficult to conduct randomized trials in patients with HCC because of ethical considerations. Moreover, it would be necessary to match the compared groups on the basis of the risk of tumor recurrence and survival. The novelty of our study is in the use of propensity score matching analysis to minimize selection bias when comparing the OS and DFS rates between patients who underwent TACE-RFA and those who underwent SR.

Our study had some limitations, however. First, our study had a retrospective approach and a nonrandomized design; therefore, the introduction of selection bias was unavoidable. Second, our study had limited statistical power to detect OS differences adjusted for confounding factors. Third, it is clear that for tumors larger than 3 cm, there is a benefit for combination therapy, but it is not clear whether adding TACE to RFA is really beneficial for tumors smaller than 3 cm (29).

We conclude that TACE-RFA is safe and may confer an OS rate comparable with that of SR after adjusting for potential confounders. However, SR improved the DFS rate compared with

that attained with TACE-RFA. Although these findings should be confirmed in prospective randomized controlled trials, our analyses suggest that TACE-RFA may be considered an alternative treatment modality in patients with early-stage HCCs when SR is not feasible.

Disclosures of Conflicts of Interest: Y.T. No relevant conflicts of interest to disclose. **H.T.** No relevant conflicts of interest to disclose. **Y. Morimoto** No relevant conflicts of interest to disclose. **N.T.** No relevant conflicts of interest to disclose. **T.K.** No relevant conflicts of interest to disclose. **Y. Makino** No relevant conflicts of interest to disclose. **H.Y.** No relevant conflicts of interest to disclose.

References

1. Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. World J Gastroenterol 2008;14(27):4300–4308.
2. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693–699.
3. Taura K, Ikai I, Hatano E, et al. Influence of coexisting cirrhosis on outcomes after partial hepatic resection for hepatocellular carcinoma fulfilling the Milan criteria: an analysis of 293 patients. Surgery 2007;142(5):685–694.
4. Poon RT. Optimal initial treatment for early hepatocellular carcinoma in patients with preserved liver function: transplantation or resection? Ann Surg Oncol 2007;14(2):541–547.
5. Lam VW, Ng KK, Chok KS, et al. Incomplete ablation after radiofrequency ablation of hepatocellular carcinoma: analysis of risk factors and prognostic factors. Ann Surg Oncol 2008;15(3):782–790.
6. Yamakado K, Nakatsuka A, Ohmori S, et al. Radiofrequency ablation combined with chemoembolization in hepatocellular carcinoma: treatment response based on tumor size and morphology. J Vasc Interv Radiol 2002;13(12):1225–1232.
7. Yamakado K, Nakatsuka A, Akeboshi M, Shiraki K, Nakano T, Takeda K. Combination therapy with radiofrequency ablation and transcatheter chemoembolization for the treatment of hepatocellular carcinoma: short-term recurrences and survival. Oncol Rep 2004;11(1):105–109.
8. Tanaka K, Nakamura S, Numata K, et al. Hepatocellular carcinoma: treatment with percutaneous ethanol injection and transcatheter arterial embolization. Radiology 1992;185(2):457–460.
9. Kim JW, Kim JH, Won HJ, et al. Hepatocellular carcinomas 2-3 cm in diameter: transarterial chemoembolization plus radiofrequency ablation vs. radiofrequency ablation alone. Eur J Radiol 2012;81(3):e189–e193.
10. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208–1236.
11. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649–655.
12. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9(4):298–304.
13. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients: SUPPORT Investigators. JAMA 1996;276(11):889–897.
14. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17(19):2265–2281.
15. Yamakado K, Nakatsuka A, Takaki H, et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology 2008;247(1):260–266.
16. Kagawa T, Koizumi J, Kojima S, et al. Transcatheter arterial chemoembolization plus radiofrequency ablation therapy for early stage hepatocellular carcinoma: comparison with surgical resection. Cancer 2010;116(15):3638–3644.
17. Vivarelli M, Guglielmi A, Ruzzenente A, et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg 2004;240(1):102–107.
18. Abu-Hilal M, Primrose JN, Casaril A, McPhail MJ, Pearce NW, Nicoli N. Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. J Gastrointest Surg 2008;12(9):1521–1526.
19. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013;31(4):426–432.
20. Yoshida Y, Kanematsu T, Matsumata T, Takenaka K, Sugimachi K. Surgical margin and recurrence after resection of hepatocellular carcinoma in patients with cirrhosis: further evaluation of limited hepatic resection. Ann Surg 1989;209(3):297–301.
21. Takaki H, Yamakado K, Nakatsuka A, et al. Radiofrequency ablation combined with chemoembolization for the treatment of hepatocellular carcinomas 5 cm or smaller: risk factors for local tumor progression. J Vasc Interv Radiol 2007;18(7):856–861.
22. Huang YH, Wu JC, Chen CH, et al. Comparison of recurrence after hepatic resection in patients with hepatitis B vs. hepatitis C-related small hepatocellular carcinoma in hepatitis B virus endemic area. Liver Int 2005;25(2):236–241.
23. Li Q, Li H, Qin Y, Wang PP, Hao X. Comparison of surgical outcomes for small hepatocellular carcinoma in patients with hepatitis B versus hepatitis C: a Chinese experience. J Gastroenterol Hepatol 2007;22(11):1936–1941.
24. Peng ZW, Lin XJ, Zhang YJ, et al. Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. Radiology 2012;262(3):1022–1033.
25. Wang JH, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. J Hepatol 2012;56(2):412–418.
26. Hung HH, Chiou YY, Hsia CY, et al. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. Clin Gastroenterol Hepatol 2011;9(1):79–86.
27. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008;47(1):82–89.
28. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? a prospective analysis of our approach. Arch Surg 1999;134(9):984–992.
29. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010;116(23):5452–5460.