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Combination therapy of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) for small hepatocellular carcinoma: comparison with TACE or RFA monotherapy

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Abstract

Purpose To compare the safety and efficacy of combined transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) for small hepatocellular carcinoma (HCC) with those of TACE or RFA monotherapy.

Methods This study included 34 combined TACE and RFA (TACE-RFA), 87 TACE, and 136 ultrasound-guided RFA, which were performed to treat HCC (≤ 3 cm, 3 or fewer) between March and August 2009. The safety (Child–Pugh score indicating hepatic functional reserve, patient discomfort requiring medication, duration of hospitalization, and complications) and efficacy (1-month, 6-month, and 1-year tumor responses) profiles of each treatment were evaluated and compared.

Results TACE-RFA group showed longer hospital stay and more frequent patient discomfort requiring medication than TACE or RFA group ($P < 0.001$). The frequency of overall complications after TACE-RFA was higher than TACE ($P = 0.006$) or RFA ($P = 0.009$). There were no statistical differences in major complication rates between the three groups ($P = 0.094$). Child–Pugh score at 1-month follow-up showed no significant difference between the three groups ($P = 0.162$). 1-month, 6-month, and 1-year tumor responses of TACE-RFA were similar to those of RFA and better than those of TACE.

Conclusions TACE-RFA appears to result in more frequent patient discomfort requiring medication, longer hospital stay, and more frequent complications than TACE or RFA monotherapy. Tumor response of TACE-RFA seems to be similar to that of RFA and better than TACE monotherapy. Thus, TACE-RFA for treating small HCC may be required for the selected patients, especially patients with small HCC ineligible for RFA monotherapy.

Keywords Hepatocellular carcinoma · Transarterial chemoembolization · Radiofrequency ablation · Safety

Introduction

Percutaneous radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) has been shown excellent therapeutic efficacies comparable to those of surgical resection [1, 2]. Local tumor control is considered to be an important factor in achieving good survival of patients treated with RFA [3], however, local tumor progression (LTP) is not infrequent [1, 4]. As tumor size increases, the rate of adjacent microvascular invasion and micrometastases, which are believed to substantially contribute to LTP following ablation, increases [5, 6]. A considerable number (19–33%) of even small tumors (≤ 3 cm) have micrometastases or microscopic satellite nodules and, although most satellite lesions are located within 1 cm from the main tumor, some (4–17%) develop beyond the 1 cm border [7, 8]. Such LTP can be reduced by creating larger ablation zone.

Combined transarterial chemoembolization (TACE) and RFA (TACE-RFA) was first introduced as one of strategies to obtain a larger ablation zone [9]. The efficacy of TACE-RFA has been proven in the treatment of small and medium-sized HCCs [10–13]. In addition, TACE-RFA can be applied for the treatment of small HCCs inconspicuous on ultrasound (US) or unenhanced computed tomography (CT), two guiding modalities most frequently used for percutaneous RFA [14]. Intratumoral retention of iodized oil used in TACE provides a radiographic contrast to those inconspicuous tumors and makes subsequent RFA feasible. Thus, it is

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expected that the TACE-RFA will be more widely applied for the treatment of HCC.

On the other hand, the safety of TACE-RFA is an important issue that should be fully investigated. Each of TACE and RFA can cause damages to the liver (i.e., liver infarction, failure, abscess, and bilopathy), and their combination may carry a risk of cumulative serious hepatic injuries [15, 16]. Previous studies have reported complications following TACE-RFA, including hepatic infarction, liver failure, bile duct stenosis, and arterial bleeding [17–19]. However, its safety has been investigated in only a few studies [20, 21], which may raise requirement of more thorough investigation on the safety issue.

In this study, we aimed to compare the safety and efficacy of TACE-RFA for small HCC with those of TACE or RFA monotherapy.

Methods

Patients

This retrospective study was approved by our institutional review board with waiver of informed consent. Between March and August of 2009, 36 TACE-RFA in 36 patients with small HCCs (≤ 3 cm) infeasible for US-guided RFA, 790 TACE in 633 HCC patients, and 159 US-guided RFA in 154 HCC patients were performed in our institution. Based on our routine practice for patients with small HCC (≤ 3 cm in size, 3 or fewer in number), US-guided RFA was considered when a patient was ineligible for surgery or due to patient's preference. TACE-RFA was considered when a patient was ineligible for US-guided RFA. TACE was considered when a patient was finally determined to be ineligible for curative treatments (i.e., RFA, TACE-RFA, and surgery). For cohort comparison of TACE-RFA, which was performed for patients with small HCC (≤ 3 cm in size, 3 or fewer in number) and by a combination of segmental or subsegmental TACE and immediately subsequent RFA, patients who underwent segmental/subsegmental TACE for small HCC (≤ 3 cm in size, 3 or fewer in number) were selected as TACE cohort, which included 107 TACE in 103 patients. As shown in Fig. 1, this comparison study excluded the following patients: (1) who underwent any other treatment within 2 weeks before and after each treatment, (2) who had hepatic arteries destroyed prior to TACE or underwent TACE solely via an extrahepatic artery, or (3) who had no laboratory data requiring for safety comparison. In six patients who underwent TACE or RFA two times, second TACE or RFA procedure was excluded from the study because repetition of same patient data could cause a bias in statistical analysis. Finally, 34 TACE-RFA in 34 patients, 87 TACE in 87 patients, and 136 US-guided RFA in 136 patients were enrolled in this study.

Patient and tumor characteristics were summarized in Table 1. Twenty-three patients in TACE-RFA group, 77 patients in TACE group, and 84 patients in RFA group had a history of previous treatment, including TACE ($n = 7$ in

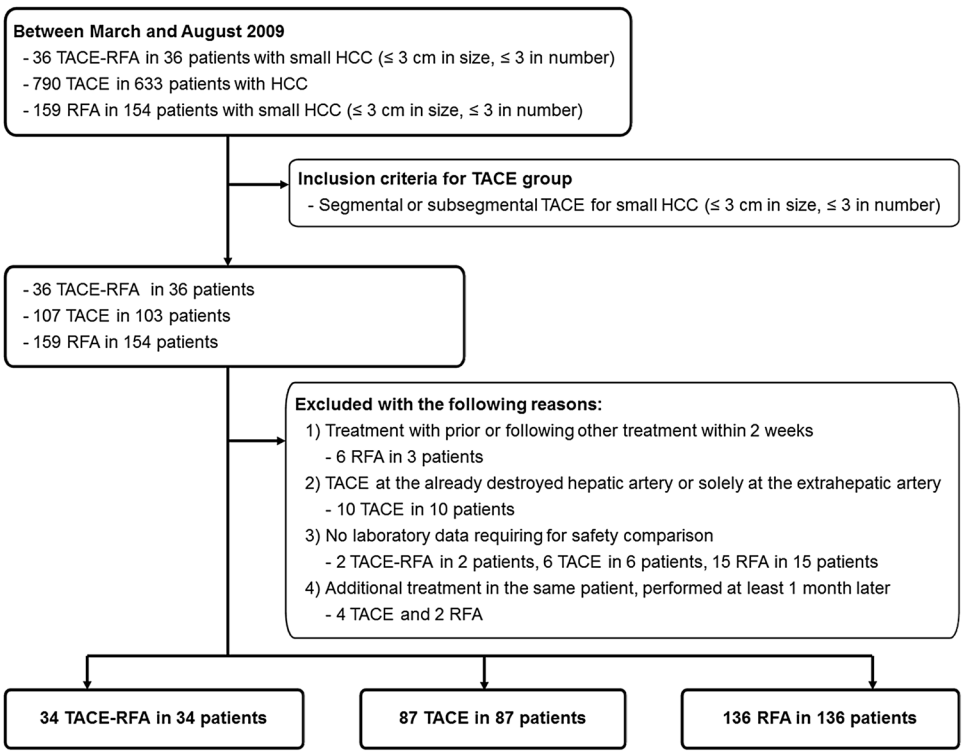

Fig. 1 A flow chart showing study group enrollment

Table 1 Baseline patient and tumor characteristics in each treatment group

	TACE-RFA ($n=34$)	TACE ($n=87$)	RFA ($n=136$)	P value
Age (mean ± SD)	57.4 ± 8.6 years	60.2 ± 9.2 years	60.2 ± 9.9 years	0.272
Sex (M:F)	27:7	65:22	102:34	0.848
Etiology (HBV:HCV:non-viral)	31:1:2	69:13:5	103:19:14	0.245
Child–Pugh class (A:B:C)	28:6:0	76:10:1	119:14:3	0.748
Previous treatment (yes:no)	23:11	77:10	84:52	< 0.001
Tumor number (one:two:three)	21:10:3	53:29:5	130:6:0	< 0.001
Sum of the size of target tumor(s)	Median, 1.8 cm (range 0.8–4.9)	Median, 2.0 cm (range 0.7–4.7)	Median, 1.8 cm (range 1.0–4.5)	0.158

TACE-RFA group; $n=26$ in TACE; $n=18$ in RFA), RFA ($n=6$ in TACE-RFA group; $n=5$ in TACE; $n=21$ in RFA), surgical resection ($n=1$ in TACE-RFA group; $n=4$ in TACE; $n=7$ in RFA), or multimodal treatment ($n=9$ in TACE-RFA group; 42 in TACE; 38 in RFA), a combination of TACE, RFA, surgical resection, percutaneous ethanol injection therapy, or radiation therapy. The diagnosis of HCC was established based on clinical criteria of the Asian Pacific Association for the Study of Liver Disease [22]. Six patients were confirmed to have a HCC by a percutaneous needle biopsy. TACE-RFA procedures were performed to treat 50 small HCCs in 34 patients, TACE to treat 126 HCCs in 87 patients, and RFA to treat 142 HCCs in 136 patients.

Treatment procedures: TACE, RFA, and TACE-RFA

On in-patient basis, all treatment procedures were performed with local anesthesia. All patients were carefully monitored with vital signs, and received administration of analgesia during the procedure; intravenous administration of 50 mg of pethidine (Pethidine; Hana pharmaceutical, Seoul, Korea) for TACE, intravenous administration of 50 mg of fentanyl (Fentanyl citrate Hana; Hana pharmaceutical, Seoul, Korea) for RFA, or continuous intravenous infusion of 0.025–0.05 μg/kg/min of remifentanil (Ultiva, GlaxoSmithKline, Parma, Italy) for TACE-RFA. All treatment procedures were performed by one of nine radiologists with at least 4 years of experience with each treatment.

TACE was performed in the following manner: Selective angiography of hepatic and mesenteric arteries was obtained to identify tumor and its arterial feeders. A coaxial 2-F (Progreat; Terumo, Tokyo, Japan) or 2.4-F (Microferret; Cook, Bloomington, IN, USA) was selectively inserted into or as close as possible to the tumor feeding artery at least to the segmental branch level. Selective TACE was performed by slowly infusing an emulsion of iodized oil (Lipiodol; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) and doxorubicin hydrochloride (Adriamycin; Dong-A Pharmaceutical, Seoul, Korea). The dose of iodized oil and doxorubicin was determined depending on the tumor size and vascularity. The tumor feeding artery was embolized with gelatin sponge pledgets (Cutanplast; Mascia Brunelli, Milan, Italy).

Percutaneous RFA was performed using an internally cooled electrode system (Cool-tip RF ablation system; Valleylab, Boulder, CO, USA or Well-point RF Electrode; STARmed, Goyang, Korea) under real-time US guidance with a single 17-gauge straight electrode with a 2- or 3-cm active tip, or a cluster of three electrodes with a 2.5-cm active tip mounted on a common handle. Active tip length was selected according to the tumor size and geometry. Ablation time was varied despite recommended time of 8–12 min. If a tumor was smaller than 1 cm or located near dangerous organ such as the colon and heart, the ablation time was reduced at the operator's discretion. Single or multiple overlapping ablations were performed to achieve an ablation zone with at least a 0.5–1.0 cm ablative margin around the tumor. After the RFA procedure, the intrahepatic needle track was cauterized during electrode retraction to prevent bleeding or tract seeding.

For TACE-RFA, the same techniques and devices as in TACE or RFA monotherapy were used. Cone-beam CT (CBCT) was routinely checked with completion of TACE to evaluate the extent of iodized oil within the tumor. Percutaneous RFA was performed immediately following TACE. A single 17-gauge straight electrode with a 2- or 3-cm active tip was inserted into the index tumor under guidance of fluoroscopy, US, CBCT, or their combination. The final location of the electrode tip was confirmed by CBCT to assure appropriate coverage of HCC by ablative zone.

All patients were observed carefully and managed according to our practice guideline. A ward nurse routinely checked every 6–8 h if a patient had any discomfort (i.e., pain, nausea, and vomiting). Pain was measured on a numeric rating scale between 0 (no pain) and 10 (worst possible pain). The patient with numeric pain rating scale ≥ 4 was managed with intravenous administration of 50 mg of pethidine. Laboratory examinations including complete blood cell count, prothrombin time, albumin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were routinely checked 1 day before

and after each treatment. Post-procedural contrast-enhanced CT was checked to assess the completeness of the ablation and detect the presence of immediate complications on the same day of RFA or the following day after TACE-RFA, which was not routinely obtained after TACE monotherapy. If there was no clinical and radiological evidence of complications requiring further management, patients were routinely discharged the following day after each treatment with drugs (acetaminophen and metoclopramide) for symptoms of post-embolization or post-ablation syndrome (including mild fever < 37.7 °C, abdominal pain, and nausea/vomiting). All patients were instructed to report any problems being aggravated even after medication or persisting for more than 1 week. All patients were followed up with contrast-enhanced CT and laboratory tests at 1 month after each treatment and, thereafter at every 3 months. When residual tumor or recurrence was detected, patients received TACE, RFA, TACE-RFA, radiation therapy, or sorafenib treatment depending on the progression or recurrence pattern and underlying liver function.

Assessment

Medical records, imaging studies, and laboratory examinations were reviewed for assessment. For safety assessment, damage to hepatic functional reserve, patient discomfort requiring medication, duration of hospitalization, and complications after each treatment were evaluated and compared between the three treatment groups. Damage to hepatic functional reserve was evaluated by analyzing Child–Pugh (CP) scores between 1 day before and 1 month after treatment. As post-embolization or post–ablation syndrome was considered a side effect of TACE or RFA, not a complication [15, 16], patient discomfort requiring medication (i.e., pain, nausea, vomiting) and duration of hospitalization after treatment were evaluated. Complications were classified according to the guidelines of the Society of Interventional Radiology [15, 16]. A major complication was defined as any event that necessitated therapy with hospitalization or involved permanent adverse sequelae, including death. All other complications were classified as minor. Tumor responses at 1-month, 6-month, and 1-year after each treatment were also evaluated and classified according to the modified Response Evaluation Criteria in Solid Tumor (mRECIST) for HCC [23].

Statistical Analysis

Continuous data between three groups were compared using one-way analysis of variance (ANOVA) or Kruskal–Wallis test. Those between two groups were compared by Mann–Whitney *U* test. When a positive result from ANOVA or Kruskal–Wallis test was encountered, Tukey's test was used for post hoc analysis. Categorical data were compared by using the Chi square or Fisher's exact test, and significant variables found in the three group comparison were further analyzed by pairwise comparison to determine which groups were different, with *P* value adjusted by Bonferroni method for multiple testing. After adjusting baseline characteristics listed in Table 1 to minimize a bias by confounding factors, CP score following each treatment was compared using generalized estimating equations, duration of hospitalization after treatment was compared by using Spearman partial correlation analysis, and patient discomfort after treatment was compared by using logistic regression analysis. All statistical analyses were performed with SPSS version 20.0 (SPSS, Chicago, IL, USA) or Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC). *P* value less than 0.05 was considered statistically significant.

Results

There were no significant differences in age, sex, etiology of underlying liver disease, CP class, and sum of the size of target tumors among the three treatment groups. However, there were significant differences in the history of previous treatment and the number of target tumors (Table 1). History of previous treatment was more frequently observed in TACE group than RFA or TACE-RFA group (vs. RFA, $P < 0.001$; vs. TACE-RFA, $P = 0.018$). TACE-RFA and TACE groups had more target tumors compared with RFA group (TACE-RFA vs. RFA, $P < 0.001$; TACE vs. RFA, $P < 0.001$).

TACE procedure of TACE-RFA group was performed at the subsegmental branch of the hepatic artery in 26 patients and at the segmental branch in 8 patients, with use of iodized oil (median, 4.0 ml; range, 2–12 ml) and doxorubicin (median, 20.0 mg; range, 10–40 mg). In TACE group, it was performed at the subsegmental branch in 74 patients and at the segmental branch in 13 patients, with use of iodized oil (median, 4.0 ml; range, 2–7 ml) and doxorubicin (median, 20.0 mg; range, 10–30 mg). The level of TACE and the amount of iodized oil used were similar between TACE-RFA and TACE groups (TACE level, $P = 0.262$; amount of iodized oil, $P = 0.093$), but more dose of doxorubicin was used in TACE group compared to TACE-RFA group ($P = 0.006$). Active tip length used in RFA for 50 tumors of TACE-RFA group was 2-cm ($n = 32$) or 3-cm ($n = 18$). Active tip length used in RFA monotherapy for 142 tumors was 2-cm ($n = 68$) or 3-cm ($n = 65$) of straight type or 2.5-cm of cluster type ($n = 9$). Median value of total ablation time of each patient was 16.0 min (range 7–41 min) in TACE-RFA group and 12.0 min (range 3–52 min) in RFA group. RF electrodes used were similar between TACE-RFA and RFA groups ($P = 0.054$), but total ablation time applied in TACE-RFA group was longer than RFA group ($P < 0.001$).

Laboratory liver function tests and CP scores before and 1 month after each treatment are shown in Table 2. There were no significant differences in baseline AST, ALT, and total bilirubin levels between the three treatment groups. There were no significant differences in baseline and 1-month follow-up CP scores between the three groups (baseline, $P=0.711$; 1-month follow up, $P=0.162$). Rise of CP score at 1-month follow-up was observed in 17.6% (6 of 34) of TACE-RFA group, 5.7% (5 of 87) of TACE, and 10.3% (14 of 136) of RFA, which showed no significant difference between the three groups ($P=0.141$). Rise of CP score at 1-month follow-up was observed in 1 of 6 baseline CP class B patients in TACE-RFA group, 2 of 10 in TACE group, and 3 of 14 in RFA group, which showed no significant difference between the three groups ($P=1.000$).

Duration of hospitalization and patient discomfort requiring medication after each treatment are summarized in Table 3. Median value of hospital stay after treatment was 1.0 day in all the three treatment groups, however, hospital stay for 2 days or longer was observed in 47% (16/34) patients undergoing TACE-RFA, 10% (9/87) patients undergoing TACE, and 8% (11/136) patients undergoing RFA. The hospital stay after TACE-RFA was significantly longer than TACE (Spearman partial correlation coefficient $r=-0.323$, $P<0.001$) or RFA ($r=-0.333$, $P<0.001$). Also, patient discomfort requiring medication was more frequently observed after TACE-RFA (91%, 31/34) than TACE (51%, 44/87) or RFA (26%, 35/136) monotherapy (vs. TACE, *odds ratio* [OR] 12.02, 95% *confidence interval* [CI] 2.52–57.35, $P<0.001$; vs. RFA, OR 34.16, 95% CI 7.27–160.52, $P<0.001$). In all the three groups, pain was

Table 2 Laboratory liver function tests and Child–Pugh score (CPS) before and 1-month after each treatment

	TACE-RFA ($n=34$)	TACE ($n=87$)	RFA ($n=136$)	*P* value	Subgroup analysis		
					TR versus *T*	TR versus *R*	*T* versus *R*
AST (U/L)							
Before Tx	38.4 ± 11.9	41.2 ± 20.7	39.5 ± 17.3	1.000	1.000	1.000	1.000
1-month FU	41.9 ± 18.0	42.6 ± 20.0	41.1 ± 22.1	1.000	1.000	1.000	1.000
ALT (U/L)							
Before Tx	37.3 ± 12.0	36.5 ± 28.1	34.3 ± 20.6	0.184	0.675	0.279	1.000
1-month FU	38.1 ± 15.2	33.6 ± 20.0	36.0 ± 26.2	0.115	0.347	0.682	1.000
TB (mg/dL)							
Before Tx	1.1 ± 0.5	1.0 ± 0.7	0.9 ± 0.6	0.393	0.936	0.177	1.000
1-month FU	1.3 ± 0.7	1.2 ± 1.2	1.1 ± 1.0	1.000	1.000	1.000	1.000
CPS							
Before Tx	5.6 ± 1.1	5.6 ± 1.0	5.6 ± 1.1	0.711	1.000	1.000	1.000
1-month FU	5.9 ± 1.3	5.4 ± 0.8	5.6 ± 1.1	0.162	0.184	0.239	1.000

Values are mean ± standard deviation

TR TACE-RFA, *T* TACE, *R* RFA, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TB* total bilirubin, *Tx* treatment, *FU* follow-up

Table 3 Duration of hospitalization and patient discomfort requiring medication after each treatment

	TACE-RFA ($n=34$)	TACE ($n=87$)	RFA ($n=136$)	Statistical analysis		
				TR versus *T*	TR versus *R*	*T* versus *R*
Hospital stay (days)[a]	1.0 (1–9)	1.0 (1–7)	1.0 (1–5)	$r=-0.323$ $P<0.001$	$r=-0.333$ $P<0.001$	$r=-0.014$ $P=0.825$
Patient discomfort	31/34 (91%)	44/87 (51%)	35/136 (26%)	OR = 12.02 95% CI 2.52–57.35 $P<0.001$	OR = 34.16 95% CI 7.27–160.52 $P<0.001$	OR = 2.84 95% CI 1.38–5.86 $P=0.002$
Pain	31/34 (91%)	33/87 (38%)	26/136 (19%)	–		
N/V	18/34 (53%)	21/87 (24%)	9/136 (7%)	–		
Fever	5/34 (15%)	1/87(1%)	2/136 (1.5%)	–		
Others		Urticaria ($n=1$)	Headache ($n=1$)	–		

[a]Values are median (minimum–maximum)

TR TACE-RFA, *T* TACE, *R* RFA, *r* Spearman partial correlation coefficient, *OR* odds ratio, *CI* confidence interval

the most frequent discomfort that patients complained of. As the longer hospitalization after TACE-RFA might be a consequence of the higher frequency of patient discomfort requiring medication, we compared again duration of hospitalization after treatment, with additional adjustment of the influence of patient discomfort. The result showed that the hospital stay after TACE-RFA was still significantly longer than TACE ($r = -0.208$, $P = 0.023$) or RFA ($r = -0.299$, $P < 0.001$).

Complications developing after each treatment are listed in Table 4. Eleven complications (32%, 11/34) occurred after TACE-RFA, 7 complications (8%, 7/87) after TACE, and 14 complications (10%, 14/136) after RFA. The frequency of overall complications was significantly higher after TACE-RFA than TACE or RFA (vs. TACE, $P = 0.006$; vs. RFA, $P = 0.009$). Most complications in all the three groups were minor. Of minor complications, subsegmental hepatic infarction was most frequently observed after TACE-RFA (5/34, 14.7%), TACE (2/87, 2.3%), and RFA (5/136, 3.7%). All minor complications did not require any special treatment. In terms of major complications, two major complications (2/34, 5.9%) occurred after TACE-RFA, including one case of liver abscess who died of acute respiratory distress syndrome secondary to septic pneumonia and the other case of hepatic encephalopathy which developed in a patient with CP score of 9 and required lactulose enema. The patient of mortality was discharged from the hospital 1 day after TACE-RFA without any specific problems despite subsegmental infarction around the ablative zone on 1-day post-procedural CT, but had fever and abdominal pain 2 days later, persisting even following oral medication of acetaminophen. He ignored the symptoms for 6 days and presented late with altered mentality. Abdomen and chest CT scans at presentation confirmed focal gas-forming abscess in the right hepatic lobe and septic pneumonia involving both lungs. He was managed with endotracheal intubation at intensive care unit and liver abscess was completely resolved at 1-month follow-up. But, he died of acute distress respiratory syndrome secondary to septic pneumonia 2 months later. Two major complications developed after TACE, including one case of hepatic abscess requiring antibiotics treatment and the other case of hepatic encephalopathy requiring lactulose enema. One case of hepatic encephalopathy was encountered after RFA, which was managed with lactulose enema. There were no statistical differences in major complication rates between the three treatment groups ($P = 0.094$).

Tumor responses at 1-month, 6-month, and 1-year after each treatment are shown in Table 5. At 1-month, complete response (CR) was observed in all the 34 TACE-RFA patients. In TACE group, CR was observed in 63 of 87 (72%) patients, partial response (PR) in 17 patients, stable disease (SD) in one patient, and progressive disease (PD) in 6 patients. In RFA group, CR was observed in 131 of 136 (96%) patients and PD in 5 patients (due to development of new tumor in other area of the liver despite complete ablation of the treated tumor). By 1-year follow-up, imaging follow-up was terminated in 11 patients: 5 patients (4 patients in TACE group and 1 patient in RFA group) were lost to follow-up, 5 patients (4 patients in RFA group and 1 patient in TACE-RFA group) died, and one patient in TACE group was transferred to local hospital near his residence. Four of the 11 patients showed CR at the last imaging study obtained before 6-month follow-up (1 patient in TACE-RFA group, 2 patients in TACE group, and 1 patient in RFA group) and they were excluded from the analysis of 6-month and 1-year tumor responses. However, the other seven patients who already showed PD at the imaging study before 6-month follow-up were included in the assessment of 6-month and 1-year tumor responses. Until 1-year follow-up, CR was observed in 76% of TACE-RFA group, 31% of TACE group, and 66% of RFA group. Both TACE-RFA and RFA groups showed higher CR rates than TACE group at 1-month (TACE-RFA or RFA vs. TACE, $P < 0.001$), 6-month (TACE-RFA vs. TACE, $P = 0.048$; RFA vs. TACE, $P = 0.039$), and 1-year (TACE-RFA or RFA vs. TACE, $P < 0.001$) follow-up. PD was observed in 8 TACE-RFA patients, 59 TACE patients, and 46 RFA patients. LTP of the target tumor was observed in 3% (1/33) of TACE-RFA

Table 4 Major and minor complications following each treatment

	TACE-RFA ($n = 34$)	TACE ($n = 87$)	RFA ($n = 136$)	P value
No of complications	11	7	14	0.002
Major complications	Liver abscess with secondary septic pneumonia causing death ($n = 1$) Encephalopathy ($n = 1$)	Liver abscess ($n = 1$) Encephalopathy ($n = 1$)	Encephalopathy ($n = 1$)	0.094
Minor complications	SS infarction ($n = 5$) SS IHD dilatation ($n = 1$) Partial thrombus in LPV ($n = 1$) Small right pleural effusion ($n = 2$)	SS infarction ($n = 2$) SS IHD dilatation ($n = 2$) Partial thrombus in MPV ($n = 1$)	SS infarction ($n = 5$) Transient IHD dilatation ($n = 3$) Colon wall thickening ($n = 2$) Perihepatic hematoma ($n = 2$) Small right pleural effusion ($n = 1$)	

SS subsegmental, *IHD* intrahepatic bile duct, *LPV* left portal vein, *MPV* main portal vein

Table 5 Tumor responses at 1-month, 6-month, and 1-year after each treatment

	1-month tumor response			6-month tumor response			1-year tumor response		
	TR ($n=34$)	T ($n=87$)	R ($n=136$)	TR ($n=33$)	T ($n=85$)	R ($n=135$)	TR ($n=33$)	T ($n=85$)	R ($n=135$)
CR	34 (100%)	63 (72%)	131 (96%)	29 (88%)	56 (66%)	109 (81%)	25 (76%)	26 (31%)	89 (66%)
Non-CR	0	24[a]	5*	4*	29*	26*	8*	59*	46*
P value	< 0.001			0.011			< 0.001		
Subgroup analysis									
TR versus *T*	< 0.001			0.048			< 0.001		
TR versus *R*	0.584			0.337			0.278		
T versus *R*	< 0.001			0.039			< 0.001		

TR TACE-RFA, *T* TACE, *R* RFA

*Cases of PD

[a]Cases including PR ($n=17$), SD ($n=1$), and PD ($n=6$)

group, 33% (28/85) of TACE group, and 7% (9/135) of RFA group.

Discussion

TACE-RFA can be performed in a single-session without time delay between TACE and RFA or in a dual-session with time interval of up to 4 weeks between the treatments [18, 24, 25]. The ablation zone in the single-session combination is assumed to be larger than the dual-session combination due to the maximized perfusion reduction by TACE just prior to RFA [26]. On the other hand, acute hepatic damage may be more severe with the single-session combination than the dual-session combination [26]. Therefore, the degree of hepatic damage after TACE-RFA can be affected by time interval between TACE and RFA. As TACE and RFA were performed in one session, the safety results in this study may represent the most severe hepatic damage that can be induced by TACE-RFA.

As both TACE and RFA can cause damages to the liver (i.e., liver infarction, failure, abscess, and bilopathy) [15, 16], cumulative hepatic damages by their combination may be a major concern. In the current study, the three treatment groups showed no significant differences in baseline and 1-month follow-up CP scores (baseline, $P=0.711$; 1-month follow up, $P=0.162$). Rise of CP score at 1-month follow-up was observed in 17.6% (6 of 34) of TACE-RFA group, which is higher than that (5.3% and 9%) of two previous studies [20, 27]. However, rise of CP score at 1-month follow-up was also observed in 5.7% (5/87) of TACE and 10.3% (14/136) of RFA groups, with no significant difference between the three groups ($P=0.141$). Koda et al. [21] reported no significant difference in deterioration of hepatic functional reserve between TACE-RFA and RFA monotherapy. In addition, in CP class B patients of this study, there were no significant differences in rise of CP score between the three treatment groups ($P=1.000$). Thus, TACE-RFA may induce deterioration of hepatic functional reserve similar to TACE or RFA monotherapy.

Overall complications occurred more frequently after TACE-RFA than TACE or RFA monotherapy (vs. TACE, $P=0.006$; vs. RFA, $P=0.009$). In addition, a 32% (11/34) overall complication rate after TACE-RFA is higher than that of previous studies [18, 19, 25, 28]. This is attributed mostly to a high frequency of subsegmental hepatic infarction (14.7%, 5/34). The high frequency of subsegmental infarction might be associated with performing TACE and subsequent RFA in one session. An animal study [26] investigating the ablation zone with two different time intervals between transarterial embolization and RFA reported that decreased arterial perfusion by the preceding transarterial embolization may have a tendency to lead to a periablation zonal infarction after RFA, unlike RFA monotherapy. However, they also reported that single-session combination could create larger ablation zone than dual-session combination. Thus, it might be better to select single-session or dual-session combination after weighing the therapeutic efficacy and safety in each case. Another possible explanation for high frequency of subsegmental infarction might be dual embolization of the portal vein and hepatic artery. Because TACE techniques used in TACE-RFA were equal to TACE monotherapy, emulsion of iodized oil and doxorubicin was intra-arterially infused until the portal vein adjacent to the index tumor was visualized, which is recommended in superselective TACE for better local tumor control [29]. Development of subsegmental infarction after TACE monotherapy (2.3%, 2/87) is thought to support this surmise. The hepatic infarction rate of RFA group is similar to the previous one [30]. As subsequent RFA plays a main role in treating HCC, TACE in the combination therapy is believed to be stopped before the portal vein near the tumor is visualized. This may reduce the development of subsegmental infarction after TACE-RFA.

The 5.9% major complication rate after TACE-RFA in this study is comparable to that (2–6.7%) in previous studies [18, 19, 28]. The frequency of major complications after TACE-RFA was not statistically different with that after TACE or RFA monotherapy ($P = 0.094$). However, given that one mortality case developed after TACE-RFA, there could be a clinically significant difference in the major complication between TACE-RFA and TACE or RFA monotherapy. The mortality might have been prevented if the patient had visited our hospital earlier because he died of acute respiratory distress syndrome associated with secondary septic pneumonia. Nonetheless, it is noteworthy that liver abscess developed in a patient with subsegmental hepatic infarction near the ablative zone on 1-day post-procedural CT. In a previous study [30] reporting the frequency of hepatic infarction after RFA, a small number (2/20, 10%) of hepatic infarction were associated with liver abscess. Thus, we believe that patients with subsegmental hepatic infarction on post-procedural CT should be observed with caution for development of liver abscess.

Shibata et al. [19] mentioned that TACE-RFA might result in increased patient discomfort and prolonged hospital stay compared to RFA, without any evaluation. Results of this study can support their surmise. In the current study, 91% (31/34) of TACE-RFA group required medication due to patient discomfort, and this frequency was significantly higher than TACE (OR 12.02, 95% CI 2.52–57.35, $P < 0.001$) or RFA (OR 34.16, 95% CI 7.27–160.52, $P < 0.001$) group. This result might be associated with use of remifentanil during TACE-RFA, which is known to have shorter half-life than fentanyl or pethidine [31]. However, this confounding effect might be reduced because patient discomfort after treatment was checked every 6–8 h. Hospital stay after TACE-RFA was also significantly longer than that after TACE ($r = -0.323$, $P < 0.001$) or RFA ($r = -0.333$, $P < 0.001$). Even after controlling the influence of the higher frequency of patient discomfort, the longer hospitalization after TACE-RFA was found to be still significant (vs. TACE, $r = -0.208$, $P = 0.023$; vs. RFA, $r = -$T0.299, $P < 0.001$). Nonetheless, there might be another confounding bias as pain and length of hospital stay could be affected by other factors, such as difference in psychological preparation for the procedure [32]. Prolonged hospitalization was not counted as a major complication in this study, even though prolonged hospitalization is considered a major complication according to the guidelines of the Society of Interventional Radiology [15, 16]. This is because patients were discharged the following day after treatment due to a shortage of beds in our hospital, which is thought to be shorter than hospital stay for a few days to a week in usual clinical practice. This can be a weakness of this study.

Regarding 1-month, 6-month, and 1-year tumor responses, both TACE-RFA and RFA groups showed CR rates of 100% and 96%, 88% and 81%, and 76% and 66%, respectively, higher than those (72%, 66%, and 31%, respectively) in TACE group. These results are similar to those in previous studies [25, 33] where TACE-RFA or RFA group showed higher CR rates and longer time to progression (TTP) compared to TACE group. On the other hand, TACE-RFA is not generally recommended as a first-line treatment of small (≤ 3 cm) HCC. This is because a prospective randomized study [19] comparing TACE-RFA and RFA in patients with small (≤ 3 cm) HCC showed no additional benefits of TACE-RFA in terms of LTP, overall survival (OS), and event-free survival rates. Similarly, our comparison results between TACE-RFA and RFA groups showed no significant differences in 1-month, 6-month, and 1-year tumor responses. Nonetheless, we believe that TACE-RFA is still required for some selected patients with small HCC, especially patients with small HCC ineligible for RFA monotherapy. According to a multicenter prospective study [34], one-quarter of small HCCs are infeasible for US-guided RFA, mostly due to tumor inconspicuity or location such as hepatic dome. TACE-RFA can be a treatment option for those tumors. Indeed, in this study, TACE-RFA was applied when a patient was ineligible for US-guided RFA. In addition, for small HCCs with a 2–3 cm diameter or in subphrenic location, previous studies showed TACE-RFA could provide better local tumor control than RFA monotherapy [12, 35–37].

This study has several limitations. First, this is a retrospective cohort comparison study. Therefore, some basic background characteristics were not fully matched. Propensity scores were estimated to adjust differences observed in baseline characteristics. But, we were not able to use propensity score analysis because balance of propensity scores was not improved even after inverse probability of treatment weight. Multivariate analysis was the only way that we could use to minimize the bias. Nonetheless, due to inherent limitation of data, we had no choice but to conduct statistical analyses of complications and tumor responses without adjustment of baseline variables. Second, post-procedural CT after TACE monotherapy was not available in this study as therapeutic results of TACE are checked on 1-month follow-up CT in our routine practice. Given that many of complications were identified on imaging studies, complication rates of TACE monotherapy might have been reduced. Third, this study excluded some patients who received one of the three treatments in the study period due to lack of laboratory data requiring for safety comparison. Therefore, there could be a selection bias. Fourth, most of this study population received previous treatment and patients with non-CR (PR, SD, and PD) at follow-up received additional treatment. These could have a confounding effect in the tumor response after each treatment. In addition, these could make other therapeutic outcomes (i.e., TTP and OS) provide

invalid information, which should have been evaluated for ideal comparison of the therapeutic efficacy. Nonetheless, lack of TTP and OS data may be a weakness of this study.

In conclusion, TACE-RFA appears to result in more frequent patient discomfort requiring medication, longer hospital stay, more frequent complications than TACE or RFA monotherapy. However, the damage to hepatic functional reserve appears to be similar between the three treatments. Tumor response of TACE-RFA seems to be similar to that of RFA monotherapy and better than that of TACE monotherapy. Thus, TACE-RFA for treating small HCC may be required for the selected patients, especially patients with small HCC ineligible for RFA monotherapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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