Combined transcatheter arterial chemoembolization and radiofrequency ablation in single-session for solitary hepatocellular carcinoma larger than 7 cm

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Abstract

Aims: To evaluate technical feasibility and treatment results of combined transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) in single-session for solitary hepatocellular carcinoma (HCC) larger than 7 cm in diameter.

Methods: Institutional review board approved this retrospective study. Written informed consent was obtained from all patients. Between June 2007 and July 2013, 87 patients (75 men, 12 women; mean age, 55.5 years ± 15.0) with solitary HCC with a mean maximum diameter of 9.5 cm ± 2.4 (range, 7.1–13.5 cm) not feasible for surgical resection underwent combined TACE and RFA in a single-session. Immediately following TACE, RFA was performed under fluoroscopy and CB-CT guidance. The primary endpoint was overall survival (OS). The secondary endpoints were technical safety and local tumor progression (LTP) rates. OS and time to progression (TTP) were analyzed with the Kaplan–Meier method. Univariate and multivariate analyses were performed to identify prognostic factors affecting OS and TTP.

Results: Technical success of combined TACE and RFA in a single-session was achieved in all patients (100%). On 1-month follow-up MRI, complete response (CR) was observed in 76 of 87 patients (87.4 %), partial response (PR) in 8 and stable disease (SD) in 3 patients. The median follow-up period was 49.5 months (interquartile range, 30.0–70.0 months). The median OS was 39 months (range, 15–86 months). The cumulative OS rates at 1, 3 and 5 years were 100%, 65.5% and 47.5%, respectively. The estimated 1, 3 and 5 year LTP rates were 0%, 29.9% and 55.2%, respectively. Univariate and multivariate analyses showed a tumor larger than 10.0 cm (P < 0.05) and presence of portal vein branch invasion (P < 0.05) led to the worst prognosis. No major complications were noted.

Conclusions: Combined use of TACE and RFA in single-session is a safe and effective option in the treatment of patients with solitary large HCC (>7 cm) not amenable to surgery.

Keywords
combined treatment, hepatocellular carcinoma (HCC), interventional oncology, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE)

1 INTRODUCTION

According to the BCLC staging system, surgical treatments and radiofrequency ablation (RFA) are regarded as potentially curative treatments for HCC but are only recommended in patients with early stage tumor. Patients diagnosed with intermediate stage HCC are candidates for transcatheter arterial chemoembolization (TACE), which has proven to control symptoms and prolong survival.
However, TACE is considered as a palliative and not a curative treatment, characterized in most instances by an unsatisfactory long-term outcome due to the inability to achieve complete tumor necrosis. Furthermore, repeated TACE is often required to completely destroy the residual tumors, but its efficacy is limited and the rate of tumor recurrence after initial remission is very high.3–5

Recently, the use of TACE combined with RFA is gaining acceptance as a therapeutic strategy for the treatment of intermediate-sized (3–5 cm) HCCs because TACE decreases hepatic blood flow to tumors, making subsequent RFA more effective.6–13 After TACE, the intratumoral retention of radio-opaque iodized oil can allow guidance for subsequent RFA by making the tumor depicted on fluoroscopy, unenhanced CT, or cone-beam CT (CB-CT).14–16

Currently, treatment of large HCC (> 7 cm) is still a challenging problem.17,18 Surgical resection provides significantly better survival than TACE for solitary large HCC regardless of tumor stage. However, only a small number of patients can receive this treatment because of the presence of unfavorable anatomy, poor hepatic reserve, or other clinical factors such as old age and comorbidities.19–22

We hypothesized that combined TACE and RFA in a single-session, in which RFA is performed immediately after TACE, can lead to better local efficacy because of the more synergistic effect of the combination of the two treatments and can improve survival for patients with large HCC. The purpose of this study is to evaluate the safety and efficiency of combined TACE and RFA in single-session for solitary HCC larger than 7 cm in diameter.

2 | METHODS

2.1 | Patients

This single-arm noncomparative study was conducted at a single center to evaluate the safety and effectiveness of combined TACE and RFA in single-session for solitary large HCC (> 7 cm) in nonsurgical candidates. Our study protocol was approved by our institutional review board. Written informed consent was obtained from all patients. Since June 2007 when cone-beam computed tomography (CB-CT) became available at our institution, instead of TACE alone for solitary large HCC, we started treating those patients with a combined TACE and RFA in which RFA was performed immediately after iodized oil TACE. Treatment assignment was decided based on the consensus at multidisciplinary conference.

Inclusion criteria for our study were as follows: (a) Diagnosis of HCC confirmed by liver biopsy or made clinically according to the American Association for the Study of Liver Diseases (AASLD) criteria.23 (b) Solitary tumor > 7 cm and less than 15 cm unsuitable for surgical resection (SR) due to various reasons. (c) Unsuitable for RFA alone due to the large size tumor, or unsuitable for TACE alone determined by the consulting physicians, or failed to control the large tumor by 1–2 sessions of TACE. (d) No abnormality in major organs, as indicated by a white blood cell count of 3000/mm³ (3 × 10⁹/L) or more, platelet count > 50 × 10⁹/L, a hemoglobin level of 8.0 g/dL or more and a creatinine level of 2.0 mg/dL or less; and (e) Eastern Cooperative Oncology Group performance status (ECOG-PS) was 0 or 1 and liver function of Child-Pugh A or B.

The excluded criteria included HCC with intrahepatic and extrahepatic metastases, main portal vein tumor thrombosis (tumor with the segmental and subsegmental portal vein branches were not contraindications in this study), high risk of thermal injury to the adjacent vessel or organs, presence of massive arterial-venous shunting identified by arterial angiography or other imaging techniques, Child-Pugh C liver profile, ECOG-PS scores ≥ 2, or uncorrectable coagulopathy.

2.2 | Assessment and follow-up

Before the combined therapy, a routine physical examination, laboratory tests and imaging studies, including ultrasonography (US), dynamic contrast-enhanced computed tomography (CT), or magnetic resonance image (MRI). The imaging studies were performed within 2 weeks before the interventional procedures.

The follow-up protocol included a routine physical examination, laboratory tests and complete blood count and measurement of tumor markers (alpha-fetoprotein [AFP], carcinoembryonic antigen and carbohydrate antigen 19-9) before discharge, and then follow-up was taken 1 month later and then every 3 months. Follow-up was performed by two physicians (Y.W. and J.Y.Y.) on an outpatient basis. Patients were followed up until loss to follow-up, death, or September 30, 2016.

Postprocedural CT with or without contrast material enhancement was performed within 1 week to assess the procedural complications. Thereafter, follow-up dynamic contrast-enhanced MRI was taken 1 month later and then every 3 months. If local tumor progression (LTP) took place, follow-up interval was rescheduled. All imaging studies were reviewed by two interventional radiologists (Z.J.W. and J.X.F., each with 10 years’ experience in abdominal imaging and interventional radiology) at the time our study started. Images were interpreted in consensus.

Technical success was defined as a completion of both TACE and RFA in one treatment session. Initial tumor response was assessed based on contrast-enhanced MRI obtained at least 1 month after the procedures, according to the modified Response Evaluation Criteria in Solid Tumor (mRECIST) for HCC as follows24: complete response (CR) was defined as the absence of any enhanced tumor areas, with serum AFP less than 20 ng/mL; partial response (PR) was defined as ≥30% decrease in the sum of the greatest dimension of the viable (enhancing) target lesions; progressive disease (PD) was defined as ≥20% increase in the sum of the greatest dimension of the enhancing target lesions, or if any new intrahepatic or extrahepatic lesions appeared; and stable disease (SD) was defined as the measured shrinkage or increase not sufficient to qualify as a PR or PD.

LTP was defined as the appearance of nodular, irregular enhancement around or within the ablation zone, that occurred at least 1 month after treatment, and evaluated based on contrast-enhanced MRI. Intrahepatic distant recurrence (IDR) was defined as the appearance of new HCCs in the untreated liver. The overall survival (OS) rate was calculated from the date of entry into the treatment to the date of death or the last follow-up. Subgroup survival analyses of
patients were also performed according to age, gender, etiology of the liver disease, Child–Pugh classification, AFP levels, tumor size, portal vein branch invasion and performance status. When recurrence or residual tumor was detected, patients received again by using the combination therapy, TACE, RFA, radiation therapy, sorafenib, or conservative management, depending on the progression or recurrence pattern, underlying liver function and the patient’s overall clinical condition. The further interventional treatment was postponed if impaired liver function had not recovered to the baseline.

The primary endpoint of our study was OS. The secondary endpoints were technical safety and LTP rate. Complications were classified according to the guidelines of the Society of Interventional Radiology. A major complication was defined as any event that resulted in additional therapy, such as an increased level of care, hospital stay beyond observational status, permanent adverse sequelae and death. All other complications were classified as minor. Postembolization syndrome is the most common side effect of TACE and was not considered a complication but rather an expected outcome.

### 2.3 TACE procedure

All procedures were performed on an in-patient basis by two senior interventional radiologists (M.Q.W. and F.Y.L., with 25 and 15 years of vascular and interventional radiology experience, respectively) at the beginning of the study period, using a therapeutic angiography unit equipped with a digital flat-panel detector system (INNOVA 4100 IQ; GE Healthcare, Milwaukee, WI, USA) and nonionic contrast medium (Visipaque 320 mg/mL; GE Healthcare). Immediately before the procedure, a single dose of prophylactic antibiotics (ciprofloxacin, 500 mg, Guangzhou Xin Pharmaceutical Co., Ltd., China) was administered to all patients on a routine basis.

After intravenous moderate sedation and local anesthesia were achieved, a 4-Fr vascular sheath (Radifocus, Terumo Corporation, Tokyo, Japan) was inserted into the right femoral artery with the Seldinger technique. Through the right femoral artery approach, visceral arteriograms (digital subtraction angiography, DSA), including the celiac axis and superior mesenteric artery with delayed imaging to evaluate the portal vein, were obtained to identify tumor and feeder(s) using a 4-Fr catheter (RH; Cordis Corporation, Miami Lakes, FL, USA). After selection of tumor feeder(s) with a 2.6-Fr microcatheter (Progreat, Terumo Corporation) at the level of the segmental or subsegmental artery, a mixture of doxorubicin hydrochloride (Adriamycin; Pharmacia & Upjohn, Peapack, NJ, USA) and iodized oil (Lipiodol; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) was infused. The amount of doxorubicin hydrochloride and iodized oil used ranged from 40 to 70 mg (mean, 55.0 mg) and 12–22 mL (mean, 15.5 mL), respectively, according to tumor size and vascularity. Then the feeder(s) were embolized with gelatin sponge pledgets (Jinling pharmaceutical Limited, Nanjing, China), which were manually cut into approximately 1-mm cubes. The endpoint of TACE was stasis of feeding arterial flow. The extrahepatic collaterals (i.e., the internal thoracic artery, the right inferior phrenic artery, omental and right renal capsular artery) supplying the tumor were also embolized, if necessary. An intra-arterial injection of 4–6 mL of lidocaine (Lidocaine HCl 2%; Chengdu First Pharma-

### 2.4 RFA procedure

After TACE, RFA is performed immediately using fluoroscopic and CB-CT guidance. Safe electrode access route was planned based on post-TACE cone-beam CT and pre-procedural enhanced CT images. The two interventional radiologists (M.Q.W. and F.Y.L.) performed RFA with moderate sedation and local anesthesia in the angiographic suite. Fentanyl citrate (Yichang humanwell pharmaceutical limited liability company, Hubei, China) was used for analgesia, and lidocaine was used for local anesthesia, with cardiac, blood pressure and oxygen monitoring. We used a multipolar RF needle (RITA Medical Systems Inc., Fremont, CA, USA) in all patients. The parameters were as follows: maximum single session ablation diameter, 5 cm; length, 15–25 cm; power, 150–200 W; ablation time, 15–20 min for > 5 cm diameter and ablation temperature, 105°C.

After an appropriate RF electrode entry site was marked on the patient’s skin, the RF electrode was placed—aiming at the iodized oil accumulated in the tumors under multiple projections of fluoroscopy and the final electrode position was confirmed by CB-CT. Usually, the RF electrode was placed in two to four different sites in the tumor depend on the basis of tumor size, shape and location; two insertions of RF electrode were performed for tumor with 7.1–10.0 cm and three or more insertions were performed for tumor > 10.0 cm in diameter. RF energy was applied for 15–20 min at each site of the tumor, according to the manufacturer’s instruction. To reduce the risk of bleeding and tumor seeding, the tract was ablated in all procedures by withdrawing an active electrode to the hepatic margin. Immediately after RFA, a hepatic arteriogram was obtained to exclude arterial bleeding.

### 2.5 Post-procedural management

The patients stayed in the hospital for 2–6 days for observation and then were discharged if without complications. Appropriate hydration was administered 2 to 3 days after the treatment. Antibiotic therapy was not continued after the procedure. Analgesics and antiemetics were administered as needed.

### 2.6 Statistical analysis

OS rates and LTP rates were estimated using the Kaplan–Meier method. The following variables were analyzed as possible prognostic factors: age, gender, etiology of the liver disease, Child-Pugh classification, AFP levels, tumor size, portal vein branch invasion, performance status (ECOG) and previous treatment. Univariate and multivariate analyses were performed using the Cox proportional hazard models. Variables with a P value < 0.2 in univariate analysis were subjected to multivariate analysis. P values of < 0.05 (two-tailed) were considered statistically significant. Statistical computer software (SPSS, ver. 22.0; SPSS Inc., Chicago, IL, USA) was used for data analyses.
RESULTS

3.1 Patients

Between June 2007 and July 2013, 1982 patients were diagnosed as HCC measuring 7.1–15 cm in maximum diameter. Of the patients, 795 were excluded because they had main portal vein thrombosis (n = 65), liver failure (n = 72), end-stage tumors (n = 494), severe comorbidities (n = 53) and 98 received targeted therapy whereas 13 refused to treatment. A total of 1008 of the patients underwent TACE alone due to ascites, anatomical position, multiple nodules or they were unwilling to receive combined therapy. A total of 179 patients underwent combined TACE and RFA in single-session for solitary large HCC (7.1–15 cm in diameter), 92 of them were excluded because they were lost to follow-up (n = 27), incomplete follow-up information (n = 46), underwent other therapy (i.e., radiotherapy, targeted therapy) in 4 weeks (n = 19). Finally, 87 patients (75 men, 12 women; mean age, 55.5 years ± 15.0 [standard deviation]; age range, 32–71 years) met the inclusion criteria and were enrolled in our study. The mean maximum tumor diameter was 9.5 cm ± 2.4 (range, 7.1–13.5 cm; Figure 1).

All patients were judged not to be surgical candidates by surgeons from the Departments of Hepatobiliary and Anesthesiologists because of an insufficient postoperative hepatic reserve in 58 (66.7%) patients, unfavorable anatomy in 12 (13.8%) and the presence of cardiopulmonary diseases in 17 (19.5%) patients. Sixty-two (71.3%) patients received the combination therapy as the initial treatment for HCC; the other 25 (28.7%) patients received it as a treatment for tumor recurrence after primary treatment such as TACE (n = 19) and RFA (n = 6). The patients’ backgrounds and tumor characteristics are presented in Table 1. All patients were followed up for more than a year after the combined treatment. The median follow-up period was 49.5 months (interquartile range, 30.0–70.0 months; mean 48.5 ± 30.0 months, range, 14–86 months).

3.2 Technical success and initial tumor response

Technical success of combined TACE and RFA in single-session was achieved in all patients (100%; Figures 2 and 3). The single-session therapy was tolerated in all patients. The mean procedure time was 115.0 min ± 25.0 (80–150 min) and the mean fluoroscopy time was 21.0 min ± 10.0 (12–33 min). The number of RF electrode insertions was two to four times (mean, 3 ± 1). The mean hospital stay after the treatment was 5.0 ± 3.0 days (3–9 days).

For TACE, the extrahepatic arterial blood supply to the tumor was observed in 59 patients (67.8%). In total, 102 collateral vessels that fed the tumors were demonstrated on DSA, including the right inferior phrenic artery (n = 48), internal thoracic artery (n = 32), omental artery (n = 11), left inferior phrenic artery (n = 4), right renal capsular artery (n = 4) and intercostal artery (n = 3). All these collateral vessels were successfully embolized.
On 1-month follow-up dynamic contrast-enhanced MRI, CR (complete coagulation necrosis of the index tumor) was observed in 76 of 87 patients (87.4%), PR in 8 patients (9.2%) and SD in 3 patients (3.5%). No intrahepatic recurrence occurred at this time. Seven patients, including five patients with PR and two with SD, received TACE subsequently. The AFP level was ≥400 ng/L in 59 (67.8%) patients (mean, 8000.0 ng/L ± 5000.0; range, 800.0–20000 ng/mL) before treatment. The AFP level decreased significantly at 1 month after treatment (mean, 5000.0 ng/mL ± 4000.0; range, 300.0–12000 ng/mL; P < 0.001) in 22 (37.3%) patients, normalized (< 20 ng/mL) in 27 (45.8%) patients and without significantly change in 10 (17.0%) patients.

### 3.3 OS rates

At the end of follow-up, 46 (52.9%) of 87 patients remained alive; 41 of the 87 patients (47.1%) died 15–72 months (mean, 37.5 months ± 29.0) after the combined treatment. The cause of death was HCC progression in 29 patients (new liver tumors developed in the untreated liver in 15 patients and both LTP and distant recurrence in 14 patients), hepatic failure without tumor progression in four patients, gastrointestinal variceal bleeding in four patients and others (stroke = 2, pneumonia = 1 and heart failure = 1) in four patients.

The median OS was 39 months (mean, 41.5 ± 25.0 months; range, 15–86 months). The cumulative OS rates at 1, 3 and 5 years were, respectively, 100% (95% confidence interval [CI], 100%), 65.5% (95% CI, 48.0–77.0%) and 47.5% (95% CI, 36.5–60.0%). Univariate analysis showed a tumor larger than 10.0 cm (P = 0.027) and presence of the portal vein branches invasion (P = 0.014) led to the worst prognosis. In multivariate analysis, tumor size < 10 cm (hazard ratio 0.516; 95% CI, 0.307–0.912; P = 0.021) and tumor without portal branch invasion (hazard ratio 0.482; 95% CI, 0.297–0.835; P = 0.012) were significant favorable factors for longer survival. The other factors, including age, gender, etiology of the cirrhosis, Child-Pugh classification, previous treatment (TACE or RFA), performance status (ECOG) and AFP levels, were not significant prognostic factors in our study (Table 2).

### 3.4 Local tumor progression

During a mean follow-up period of 48.5 ± 32.0 months, tumor progression was observed in 47 of 87 patients (54.0%). LTP was found in 35 patients (40.2%), in whom distant recurrences were associated in 19 patients. Another 12 patients (14.8%) experienced distant recurrences in the untreated liver.

The estimated 1-, 3- and 5-year LTP rates was 0% (95% CI, 0 and 0), 29.9% (95% CI, 11.5 and 50.0) and 55.2% (95% CI, 32 and 80.5), respectively. The rates of 3- and 5-year LTP were 20.0% and 40.5%, respectively, in tumors < 10 cm and 37.0% and 70.5% in tumors > 10 cm in diameter. The LTP rate of tumors 7.1–10.0 cm was significantly lower than that of tumors larger than 10 cm in diameter (P = 0.035). The rates of 3- and 5-year LTP were 31.5% and 51.0%, respectively, in tumors without portal vein branches invasion and 45.5% and 87.5% in tumors with portal vein branches invasion. The LTP rate of tumors with portal vein branches invasion was significantly higher than that of tumors without portal vein branches invasion (P = 0.023).

### 3.5 Treatment of recurrent tumors

Among the 47 patients with tumor recurrences during the follow-up period, 15 (31.9%) patients underwent TACE plus radiation therapy, 10 (21.3%) patients underwent TACE plus sorafenib therapy, 5 (10.6%) patients underwent repeat the combination therapy, 12 (25.5%) underwent TACE alone and the remaining 5 (10.6%) patients received sorafenib alone. Therefore, combination therapy was the most frequent therapeutic option used for the treatment of recurrent tumors.

### Table 1: Patient background and tumor characteristics

| Parameter                     | Value          |
|-------------------------------|----------------|
| Age (years)                   | Mean ± standard deviation 55.5 ± 15.0, >60 76 (87.36), ≤60 11 (12.64) |
| Gender                        | Male 75 (86.21), Female 12 (13.79) |
| Cause of cirrhosis            | Hepatitis B virus 81 (93.10), Hepatitis C virus 6 (6.90) |
| Child–Pugh class              | A 81 (93.10), B 6 (6.90) |
| Previous treatment            | No 62 (71.26), Yes 25 (28.74) |
| Maximum tumor diameter (cm)   | Mean ± standard deviation 9.5 ± 2.4, 7.1–10 cm 66 (75.86), >10 cm 21 (24.14) |
| Tumor with portal branch invasion | Segmental branch 3 (4.5), Subsegmental branch 7 (8.05), No 77 (88.51) |
|AFP level (ng/L)               | ≥400 59 (67.82), <400 28 (32.19) |
| Tumor location                | Right lobe 52 (59.78), Left lobe 9 (10.35), Both the right and left lobes 26 (29.89) |
|Performance status             | ECOG 0 80 (91.95), ECOG 1 7 (8.05) |

Note: Data in parentheses are percentages. AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group.
FIGURE 2  Images in a 47-year-old man with single large HCC (9.5 cm in diameter), with an α-fetoprotein (AFP) level of 24,000 µg/mL at the diagnosis. He received the combination therapy as the initial treatment for HCC (A–F). (A) A portal phase computed tomography (CT) image shows a large hepatocellular carcinoma (HCC) in the right lobe (arrows). (B) Celiac-hepatic arteriography obtained before embolization shows a large HCC in the right lobe (arrows). (C) Celiac-hepatic arteriography obtained post embolization immediately shows accumulation of lipiodol in the tumor (arrows). (D) Radiography obtained during radiofrequency ablation (RFA) shows the RF electrode placed in the iodized oil accumulated in the tumor (arrows), guided by fluoroscopy. (E) Cone-beam computed tomography (CB-CT) image with coronal MIP reformat obtained during RFA shows the position of the RF electrode (arrows). In this case, second insertion was needed to ablation the lower part of the tumor. (F) Follow-up contrast-enhanced MRI obtained at 48 months after the combined treatment shows complete coagulation necrosis of the tumor and decrease in tumor size remarkably (arrows). His AFP level decreased to normal range (< 20 ng/L) at 1 month after the treatment [Colour figure can be viewed at wileyonlinelibrary.com]

3.6 | Complications

No procedure-related major complications occurred. Post treatment syndrome, characterized by some degree of abdominal pain, low-grade fever, loss of appetite, nausea and leukocytosis developed in all patients within 1 week after the combined treatment; these symptoms were self-limited and reversible and some patients received antiemetics, nonopioid analgesic and antipyretics.
An increase in liver enzymes (aspartate amino transferase [AST], alanine amino transferase [ALT]) to nearly twice the normal levels was observed 24 h after the procedures. In all cases, the enzyme levels returned to within normal limits after 1–2 weeks without specific treatment. An increase levels of serum creatinine (normal range, 44–133 μmol/L) and urea nitrogen (normal range, 2.86–7.14 mmol/L) slightly was observed in 7 patients (8.1%) at 1–5 days after the treatment, with 148 μmol/L ± 10 (range, 136–150 μmol/L) and 9.5 mmol/L ±2.0 (range, 7.6–11.0 μmol/L), respectively; these values returned to pretreatment levels at measurements 7–14 days without special treatment exception of the moderate hydration therapy.

4 | DISCUSSION

Several studies have evaluated a multimodal approach to increasing the effectiveness of single treatments for intermediate stage HCC. The available data suggest that combined therapy with TACE and RFA is...
superior to RFA or TACE alone in preventing the incomplete necrosis of HCC and in improving patient survival.\(^6\)\(^-\)\(^{10,13-17}\) However, few studies have reported combination of TACE and RFA for HCC larger than 7 cm in diameter.\(^12\)\(^,\)\(^{26,27}\) In an early study by Tateishi et al.,\(^26\) the 5-year survival rate in patients with large HCCs was 33.6% after combination of TACE and RFA, although they did not specifically examine details such as patients’ backgrounds and LTP. Takaki et al.\(^{27}\) reported that the cumulative survival rates at 1, 3 and 5 years were 100%, 62% and 41%, respectively, after combination of TACE–RFA in patients with HCCs larger than 5 cm (mean 6.2 cm, range 5.1–10 cm). In our study, OS rates at 1, 3 and 5 years were 100%, 65.5% and 47.5%, respectively, and better than the previous study. In addition, the 5-year OS rates in our study were comparable to those from SR (28–44%).\(^{21,28,29}\) Better results in our study might come from the combined TACE and RFA in single session, in which RFA is performed immediately after TACE without interval between the two treatments, and relatively good liver function (patients with Child-Pugh A in 93.1%).

In our study, the estimated 1-, 3- and 5-year LTP rates was 0%, 29.9% and 55.2%, respectively. The LTP rates after combined TACE for RFA for HCC reportedly depends on tumor size. The 3-year LTP rates are reported to be 0–8% in small HCCs (≤3 cm) and 25% in intermediate-sized HCCs (3.1–5 cm) after RFA combined with TACE.\(^{30}\) Kang et al.\(^{31}\) reported that a 3-year LTP rate was 7.7% in tumor size < 3 cm and 26.2% in tumor diameter of 3–5 cm after treatment with single-session combined TACE and RFA (P < 0.05). Another study by Morimoto et al.\(^{32}\) reported that LTP occurred in 14.3–20% of patients with HCCs ≤3 cm and in 39% of patients with HCCs 3.1–5 cm at 3 years with combination TACE and RFA. Data related to LTP rates in patients with large HCC (>7.0 cm) following the combination treatment are rare in the literature.\(^{11,13,33}\) In our study, the estimated 1-, 3- and 5-year LTP rates was 0%, 29.9% and 55.2%, respectively. Given that HCC treated in our study was larger than 7 cm in diameter (7.1–13.5 cm), the LTP rates shown in our study are acceptable.

Based on our experience, the combined TACE and RFA in single session, in which RFA is performed immediately after TACE, seems feasible for HCC larger than 7 cm not amenable to surgery. Currently, there has been no consensus about the time interval between TACE and RFA for balancing local therapeutic efficacy and safety.\(^{13}\) In several published papers related the combined therapy, TACE and RFA were performed during different sessions, separated by a time interval of 1–3 weeks.\(^6\)\(^-\)\(^ {14}\) Choe et al.\(^{34}\) suggested that the time interval between TACE and RFA should be chosen carefully to achieve a balance between successful tumor destroy and adequate preservation of liver function. The time intervals are based on the assumption that the effect of TACE would last until the time of RF ablation.\(^{13}\) However, numerous variables may affect the duration of the embolization effect, including characteristics of tumoral vascularity, the presence of an arteriovenous shunt, the severity of cirrhosis, the collaterals establishment and the embolic materials used in chemoembolization. Based on our experience, establishment of collaterals may occur at 1 week or even 24 hours after embolization and lead to decreasing the effectiveness of RFA; therefore, the embolization effect might not be optimal at the time of RFA. In addition, the interval between the treatments may prolong the hospital stay and increase the number of admissions. Considering these theoretical mechanisms, it might be desirable to perform RFA immediately after TACE, when the hepatic arterial embolic effect is expected to be at its maximum.

Large HCCs are usually fed by multiple feeding arteries, not only through the hepatic arterial branches but also through extrahepatic collaterals, and these collaterals may make it difficult to achieve complete necrosis of large tumors by TACE.\(^{35-37}\) In a report by Chung et al.,\(^{35}\) the rate of extrahepatic blood supply at the initial TACE session in a tumor > 4 cm was less than 3%; this increased to 63% when the tumor was larger than 6 cm in diameter. For the treatment of HCC to be more effective with RFA subsequently, not only the hepatic arterial branches but also these collaterals should be adequately embolized.\(^{37}\) In our study, the extrahepatic arterial collaterals supplying the tumors were demonstrated in 68% of patients during TACE procedures, mainly through the right inferior phrenic artery and the internal thoracic artery. We embolized these collaterals successfully without any complications.

No major complications were observed in our study. Currently, the combined TACE and RFA in single-session has rarely been performed in the treatment large HCC,\(^{13}\) because of concerning about the risk of complications such as hepatic arterial bleeding and hepatic dysfunction.\(^{9,20}\) Theoretically, the rate of complications should

### TABLE 2 Uni- and multivariate analyses of the factors associated with overall survival

| Variables | Univariate analysis | Multivariate analysis |
|-----------|---------------------|----------------------|
|           | Hazard ratio (95% CI) | P             |
|           |                      | Hazard ratio (95% CI) | P             |
| Age (years, ≤60 vs < 60 years) | 1.042 (0.795, 1.264) | 0.681 |                      |
| Gender (male vs female) | 1.169 (0.871, 1.661) | 0.712 |                      |
| Cause of cirrhosis (HBV vs HCV) | 1.127 (0.645, 2.014) | 0.918 |                      |
| Child-Pugh class (A vs B) | 0.946 (0.678, 1.352) | 0.412 |                      |
| AFP (ng/L, ≥400 vs < 400) | 1.247 (0.774, 1.725) | 0.796 |                      |
| Tumor size (cm, ≤10 vs > 10) | 0.579 (0.319, 0.917) | 0.027 | 0.516 (0.307, 0.912) | 0.021 |
| PV branch invasion (yes vs no) | 0.5224 (0.329, 0.875) | 0.014 | 0.482 (0.297, 0.835) | 0.012 |
| Previous treatment (yes vs no) | 1.126 (0.813, 1.439) | 0.549 |                      |
| Performance status (ECOG, 0 vs 1) | 1.269 (0.737, 1.876) | 0.817 |                      |

AFP, α-fetoprotein; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis B virus; PV, portal vein.
be higher in the combined TACE and RFA than that of TACE or RFA monotherapy.38 However, the common procedure-related complications of the combined therapy such as hepatic infarction, biloma, abscess and hepatic arterial bleeding, reported by others,27,31,34,39 did not occur in our study. In our study, posttreatment syndrome and transient increase in liver enzymes slightly were observed in all patients within 1 week after the treatment, which were comparable with those reported in other studies8–11; these symptoms were usually self-limited and reversible without special treatment. Interestingly, an increase levels of serum creatinine and urea nitrogen slightly, indicating the renal function impaired, was observed in 7 patients (8.1%) at 1–5 days after the combined treatment. Appropriate hydration was administered for these patients and these abnormal returned to the baseline levels within 2 weeks. Therefore, the combined single-session treatment could be considered a safety treatment modality in patients with large HCC.

Our study has several limitations. First, the study design was a single-arm noncomparative study conducted at a single center. Multicenter comparative studies between one single session and sequential treatments (i.e., RFA at 2–3 weeks following TACE) or TACE alone are need in the future. Second, there might be a selection bias because only a part of our patients with large HCC infeasible for SR were referred for the combination of TACE and RFA. Third, 47 patients with tumor recurrences during the follow-up period received nonelective treatments such as TACE, RFA, radiation therapy, or sorafenib therapy. These treatments might have biased the LTP of index tumors. Finally, combination of TACE and RFA in single-session was attempted in these patients regardless of results of TACE in our study. RFA in patients with successful TACE (i.e., dense accumulation of lipiodol in the tumors) might be unnecessary.

In conclusion, the results of our study demonstrate that the combined use of TACE and RFA in single session is a safe and effective option in the treatment of patients with large HCC (> 7 cm) not amenable to surgery. The combined therapy provided good local tumor control and OS, compared with previous reports using SR or TACE monotherapy and did not increase complications any more than established local treatments. Additional advantages of the single-session combined therapy include the ability to treat tumors that are not feasible for stand-alone RFA. However, our data are preliminary, and further controlled studies should verify the efficiency, safety and cost-effectiveness of single-session combined therapy for large HCC.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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