Long-term outcomes of combined transarterial chemoembolization and radiofrequency ablation versus RFA monotherapy for single hepatocellular carcinoma ≤3 cm: emphasis on local tumor progression

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ABSTRACT

Purpose: To compare the long-term outcomes of combined transarterial chemoembolization and radiofrequency ablation (TACE-RFA) with radiofrequency ablation (RFA) monotherapy for small (≤3 cm) hepatocellular carcinomas (HCCs).

Methods: A total of 248 patients with 329 HCC nodules who underwent TACE-RFA or RFA monotherapy as the only first-line treatment between January 2009 and December 2020 were included in this study. The technical success, complications, survival rate, and local tumor progression (LTP) rate were compared between the two treatments.

Results: The 1-, 3- and 5-year survival rates were similar between the two groups (98.7%, 93.0% and 75.9% vs 97.4%, 88.0% and 77.4%; p = 0.444). The 1-, 3-, and 5-year cumulative LTP rates were significantly lower in the TACE-RFA group than in the RFA monotherapy group (2.9%, 9.2%, and 13.8% vs. 5.2%, 17.0%, and 21.0%; p = 0.043). Subgroup analyses suggested that TACE-RFA showed significantly lower LTP rates than RFA monotherapy for small HCC with tumor size >2 cm (p = 0.008), subphrenic location (p = 0.021), and perivessel (p = 0.030). Furthermore, HCC with well-defined lipiodol deposition in the TACE-RFA group showed better local tumor control than the small HCC in the RFA monotherapy group (p = 0.013). There was no significant difference in the technical success rates (p = 0.064) and complication rates (p = 0.952) between the two groups.

Conclusions: TACE-RFA is superior to RFA monotherapy in providing local tumor control for small HCC with tumor size 2–3 cm in diameter, subphrenic location, perivessel and HCCs with well-defined lipiodol deposition by TACE before RFA.

1. Introduction

Minimally invasive percutaneous radiofrequency ablation (RFA) has been well established as the first-line treatment option for patients with early-stage hepatocellular carcinomas (HCC), given that it provides consistent local tumor control comparable to surgical resection [1–4]. Local tumor progression (LTP) develops from residual cancer cells after ablation, which adversely impacts patient survival outcomes [5,6]. As RFA becomes more widely available and applied for small HCCs (≤3 cm), an increased incidence of LTP has also been observed [7,8]. Therefore, to reduce LTP, the achievement of sufficient ablative margin beyond the tumor has been recommended [9,10]. However, even for small HCC, several tumor characteristics such as unfavorable tumor location (e.g., subphrenic location or periportal location), the presence of microscopic satellite lesions, or micrometastases around the primary tumor may result in difficulty in creating an appropriate and optimal ablation zone by RFA monotherapy [11,12].

The combination therapy of transarterial chemoembolization (TACE) and RFA (TACE-RFA) has been recognized to allow the creation of larger ablation zones and reinforce anti-cancer effects when compared with RFA monotherapy, leading to an improvement in local tumor control and survival in patients with medium- and large-size HCC [13,14]. Although several studies have reported using the combined therapy for small HCCs, it remains unclear whether TACE-RFA is superior to RFA monotherapy for HCCs of ≤3 cm due to several design limitations of previous studies. In particular, prior studies have primarily included tumor size of beyond 3 cm, while the long-term outcome is also lacking in studies comparing the efficacy of the two therapeutic options for small HCC (≤3 cm) [15–17]. Therefore, this study aimed to evaluate and compare the long-term outcomes of TACE-RFA and RFA monotherapy in patients with HCCs ≤3 cm.

2. Materials and methods

2.1. Patients

All HCC patients treated with RFA and TACE between January 2009 to December 2020 were retrospectively identified. The inclusion criteria of this study were as follows: (1) The
maximum diameter of each HCC lesion was ≤3 cm; (2) No evidence of vascular invasion or extrahepatic metastasis before the initial treatment; (3) All HCC lesions were treated with either the combination of TACE and RFA (TACE followed by RFA) or RFA monotherapy as the only first-line treatment. Patients who were lost to follow-up after the initial treatment were excluded. HCCs were diagnosed based on the histopathology or the American Association for the Study of Liver Diseases criteria [18]. The collection of follow-up data was completed on 30 April 2021. This study was approved by the institutional review board of our hospital, and written informed consent was obtained from all patients before treatment.

2.2. Transarterial chemoembolization procedure

Angiography of the abdominal vessels was performed via transfemoral access to identify tumor-feeding arteries, which were then catheterized supra-selectively using a coaxial microcatheter. An appropriate volume of emulsion comprised of 10–30 mg of doxorubicin in 5–10 ml of lipiodol (Guerbet, Villepinte, Seine-Saint-Denis, France) was injected slowly under continuous fluoroscopic guidance until blood flow in the tumor feeding artery had ceased. After TACE, cone-beam computed tomography (CBCT) acquisition using C-arm angiography was performed to visualize intratumoral lipiodol deposition. The time interval between TACE and RFA was usually within 30 days, depending on the patient’s physical condition and the embolization effect of intratumoral iodized oil. Concurrent RFA following TACE was performed when targeted HCCs were visible enough after TACE under fluoroscopy.

2.3. Radiofrequency ablation procedure

RFA was performed under the guidance of multi-imaging modalities, including Ultrasound (US)+computed tomography (CT) (US/CT-guided RFA) and US+CBCT (US/CBCT-guided RFA). Following the administration of local anesthesia (10–15 ml 2% lidocaine) and intravenous analgesia (Remifentanil, 0.05 μg/kg-min), an electrode needle was introduced into the target tumor under the US guidance. Then, CT/CBCT was used to confirm the final location of the electrode tip to ensure appropriate coverage of HCC by the ablative zone. The RITA Medical Systems (RITA 1500X RF generator, RITA Medical Systems; AngioDynamics, Manchester, Ga) was used according to the manufacturer’s standard recommendations for radiofrequency power settings and ablation times. A 14 Gauge or 17 Gauge electrode needle was usually selected (starburst xl, Rita Medical System; Vascular Dynamics), depending on the tumor size and anatomical location. The real-time US was used to monitor the progression of tumor ablation. Multiple overlap procedures using CT/CBCT scans were performed during the RFA in order to ascertain the creation of a sufficient ablation zone. The puncture tract was ablated during electrode retraction to prevent bleeding or tract seeding.

All procedures were performed by the same team consisting of six physicians with at least 10 years of experience in performing percutaneous RFA and TACE.

2.4. Treatment assessment and follow-up

A contrast-enhanced multiphase CT or MR was performed within 4 weeks following RFA to assess for any residual tumor. In the presence of residual tumor, immediate RFA was performed until the target lesion had achieved complete ablation. In the absence of residual tumor, subsequent follow-ups (including contrast-enhanced CT/MR and laboratory examinations) were repeated every 3 months for 2 years following RFA, then continued at 3–6-month intervals according to the risks of recurrences. If new HCC or tumor recurrence was identified during the follow-up visits, options of further optimal treatment including ablation, surgical resection, liver transplantation, TACE, systemic therapy, radiation therapy or combination therapy was instituted according to the clinical practice guidelines or multidisciplinary team discussion and the general condition of the patient. In this instance, RFA or combined with TACE was preferred to treat the residual tumor, LTP or new HCC foci.

2.5. Definitions of terminology

Technical success was defined as an absence of radiological evidence of residual tumor on the contrast-enhanced multiphase CT or MR within 4 weeks following the initial RFA. Treatment effectiveness after RFA was determined according to the modified Response Evaluation Criteria in Solid Tumor (mRECIST) for HCC [19]. Local tumor progression was defined as the occurrence of a new tumor at the edge of the ablation zone, which was considered completely ablated according to the imaging criteria [20]. Major complications were defined as any event that leads to increased patient care, hospital stay beyond observation status, and permanent adverse sequelae or death. Perivessel HCC was defined as the HCC adjacent to the intrahepatic vessels (including the first to third branches of the portal vein, first and second branches of hepatic veins or inferior vena cava), which were located within 5 mm in distance from the border of the HCC [9]. Well-defined lipiodol deposition is defined as sufficient intratumoral lipiodol deposition, which can be visible during RFA to provide a clear contrast to the surrounding liver parenchyma. Ill-defined lipiodol deposition is defined as insufficient intratumoral lipiodol deposition, which could provide a poor contrast to the surrounding liver parenchyma during RFA.

2.6. Statistical analysis

The Student’s t-test (parametric test) or Mann–Whitney U test (non-parametric test) was used to compare continuous or categorical variables, respectively. The overall survival rate was evaluated using the Kaplan–Meier method and compared with the log-rank test. The local tumor progression rate was also evaluated using the Kaplan–Meier method but compared with the Generalized Wilcoxon test. The proportional hazard model was evaluated by the proportional-hazards assumption test and Schoenfeld residual test. Cox regression models were used to analyze factors associated
with local tumor progression, including tumor size (≤20 vs. >20 mm), tumor location (non-subphrenic, subcapsular vs. subphrenic vs. subcapsular), perivessel HCC, hypervascular HCC, and AFP (<40 vs. ≥40 ng/ml). All statistical tests were two-sided and analyses were conducted using the SPSS package (version 21.0, SPSS) and GraphPad Prism 8.0.1 (244). A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 248 patients with 329 HCC nodules were included in this study. Of these, 164 patients with 225 HCCs underwent TACE followed by RFA (TACE-RFA group), while 84 patients with 104 HCCs underwent RFA monotherapy (RFA monotherapy group) as the only first-line treatment (Table 1). No significant difference was observed in the mean age, gender ratio, tumor etiology, tumor size, Child–Pugh score, BCLC stage, and proportion of patients with elevated serum α-fetoprotein between the two groups.

### Table 1. Comparisons of baseline characteristics between patients in the TACE-RFA group and the RFA monotherapy group.

| Clinical features | TACE-RFA (164 patients, 225 HCCs) | RFA (84 patients, 104 HCCs) | p-Value |
|-------------------|----------------------------------|-----------------------------|---------|
| Age (years)       | 58.5 ± 10.8 (26–88)              | 59.0 ± 10.9 (33–85)         | 0.887   |
| Gender            |                                   |                             | 0.364   |
| Male              | 133 (81.1%)                      | 72 (85.7%)                  |         |
| Female            | 31 (18.9%)                       | 12 (14.3%)                  |         |
| Liver disease type| Non-hepatitis 13 (7.9%)          | 8 (9.5%)                    | 0.238   |
|                  | Hepatitis B/C 140 (85.4%)        | 72 (88.1%)                  |         |
|                  | Other hepatitis 11 (6.7%)        | 7 (2.4%)                    |         |
| AF/FP <40 ng/mL   | 112 (68.3%)                      | 55 (65.5%)                  | 0.655   |
| AF/FP ≥40 ng/mL   | 52 (31.7%)                       | 29 (34.5%)                  |         |
| Child-Pugh score  | A 158 (96.3%)                    | 78 (92.9%)                  | 0.227   |
|                  | B 6 (3.7%)                       | 6 (7.1%)                    |         |
| BCLC stage        | A 120 (73.2%)                    | 59 (70.2%)                  | 0.554   |
|                  | B 44 (26.8%)                     | 25 (29.8%)                  |         |
| Tumor diameter(cm)| 1.90 ± 0.68 (1.0–3.0)           | 1.83 ± 0.64 (0.9–3.0)       | 0.481   |
|                  | <2.0 120 (53.6%)                 | 49 (47.1%)                  |         |
|                  | 2.1–3.0 104 (46.4%)              | 55 (52.9%)                  |         |
| Number of tumors  | 1 123 (75.0%)                    | 67 (79.8%)                  | 0.341   |
|                  | 2 29 (17.7%)                     | 14 (16.7%)                  |         |
|                  | ≥3 12 (7.3%)                     | 3 (3.6%)                    |         |

3.2. Technical success and complications

After the initial treatment, the technical success rate was 99.1% (223/225) in the TACE-RFA group and 96.2% (100/104) in the RFA-alone group, (p = 0.064). There were five target tumors that were treated with additional RFA due to residual unablated tumors identified by the contrast-enhanced CT within 4 weeks of initial treatment. Among these residual tumors, 2 tumors in each group were due to incomplete ablation, while 1 tumor in the RFA monotherapy group was the result of mistargeted ablation. All residual tumors were successfully treated with immediate additional RFA sessions.

During the perioperative period after treatment, one patient in the TACE-RFA group developed a hepatic abscess and another experienced a biloma. Both patients completely recovered after percutaneous drainage and antibiotic treatment. In the RFA monotherapy group, one patient developed pneumothorax and recovered after percutaneous drainage. The major complication rate was 1.2% (two of 164 patients) in the TACE-RFA group and 1.0% (one of 104 patients) in the RFA monotherapy group (p = 0.952). Overall, there was no treatment-related hospital mortality.

3.3. Overall survival

The median follow-up periods were 46 ± 26 months (range: 6–154 months) in the TACE + RFA group and 47 ± 25 months (range: 8–104 months) in the RFA monotherapy group. The overall 1-, 3- and 5-year survival rates were 98.7%, 92.6% and 76.6% in the TACE + RFA group and 96.3%, 88.7% and 73.9% in the RFA monotherapy group, respectively (p = 0.444) (Figure 1).

3.4. Local tumor control

LTP was identified in 20 of 225 (8.9%) tumors in the TACE + RFA group and 17 of 104 (16.3%) in the RFA group during the follow-up period. The median times of the LTP were 16.0 months (ranged 6–55 months; mean: 21.8 months) and 15.0 months (ranged 5–59 months; mean: 19.4 months) in the TACE + RFA group and the RFA monotherapy group, respectively. The 1-, 3-, and 5-year cumulative LTP rates were significantly lower in the TACE + RFA group (2.9%, 9.2% and 13.8%, respectively) than that in the RFA group (5.2%, 17.0% and 21.0%, respectively) (p = 0.003; Figure 2). The results of the proportional-hazards assumption test revealed that the local tumor progression rate met the proportional hypothesis. The hazard ratios of LTP among HCCs > 2 cm were significantly lower in the TACE-RFA group when compared with the RFA group (HR = 0.221, 95% CI = 0.083–0.586, p = 0.008; Figure 3), while no significance was observed between the groups in the hazard ratios of LTP among HCC ≤ 2 cm (HR = 0.400, 95% CI = 0.084–1.908, p = 0.181; Figure 4). When compared with the RFA monotherapy group, the hazard ratios of LTP among subphrenic HCCs (HR = 0.152, 95% CI = 0.031–0.755, p = 0.021) and perivessel HCCs (HR = 0.194, 95% CI = 0.044–0.852, p = 0.030) were significantly lower in the TACE-RFA group than in the RFA monotherapy group. In addition, in the subgroup analysis of lipiodol deposition, HCCs with well-defined lipiodol deposition tended to provide better local tumor control than those HCCs with ill-defined lipiodol deposition or without TACE. HCCs with well-defined lipiodol deposition in the TACE-RFA group showed significantly lower LTP rates than those HCCs in the RFA monotherapy group (HR = 0.342, 95% CI = 0.147–0.794, p = 0.013). At the same time, there was no significant difference between those HCCs with ill-defined lipiodol deposition and HCCs without TACE (HR = 0.946, 95% CI = 0.451–1.984,
p = 0.883). While there was no significant difference in the hazard ratios of LTP in the other subgroups between the two groups (Table 2).

4. Discussion

To compare the efficacy of RFA monotherapy and TACE + RFA in the treatment of early HCC, a reasonable inclusion criterion of ‘early HCC’ should be first established according to the applicability of RFA. Due to the high frequency of residual lesion, the usefulness of RFA is limited in the treatment for HCC larger than 3.0 cm in diameter, while TACE-RFA could provide a contrary effect. Therefore, patients with HCC ≤3 cm are the best candidates to compare the effectiveness of the two treatments for early HCC. Meanwhile, those patients with solitary HCC of 3–5 cm in diameter should be excluded. In this study, we compared the long-term outcomes of TACE + RFA with RFA monotherapy focused on those patients with HCC ≤3 cm in diameter. Our results suggested that TACE-RFA may provide better local tumor control than RFA monotherapy for HCC ≤3 cm in diameter, although survival outcomes were similar. Importantly, selected patients could benefit more from TACE-RFA than RFA monotherapy, such as those HCCs of 2–3 cm in diameter, subphrenic HCCs, and those HCCs with peritumoral vessels or well-defined lipiodol deposition by TACE before RFA.

The combination therapy of performing TACE following RFA should be regarded as one of the modified ablation strategies that prove to provide a more effective treatment for medium and large HCCs when compared with RFA monotherapy [21,22]. However, it remains debatable if this combination therapy is also more effective for HCC ≤3 cm, given that several studies have suggested no advantage in improving local tumor control and survival rate for treating in small HCCs [5,23,24], while more recent retrospective studies have shown otherwise [15,25]. Consistent with our findings, previous studies have shown that the 1-, 3-, and 5-year rates of LTP after RFA monotherapy for small HCCs were 1.4–9.7%, 3.2–21.4%, and 3.2–27.0%, respectively [9,26–28]. In particular, Shiina et al. have reported the best local tumor control for small HCCs after RFA, in which the 1- and 5-year rates of LTP were 1.4% and 3.2%, respectively, possibly attributed to the multiple overlapping ablations to obtain a larger ablation zone [26]. In our study, the 1-, 3-, and 5-year cumulative LTP rates in the TACE-RFA group were 2.9%, 9.2% and 13.8%, respectively, which was superior to RFA monotherapy in ensuring local tumor control, especially in HCCs of 2–3 cm in diameter. Similar outcomes have also been reported that surgical resection resulted in better local tumor control for HCC ≥2 cm than RFA monotherapy [29,30].
Therefore, TACE-RFA represents an effective treatment option, which is superior to RFA monotherapy in patients with HCCs of 2–3 cm.

While multiple RCTs have demonstrated equipoise between resection and RFA in HCCs <3 cm, there is some concern that small HCCs in challenging locations (such as the HCC located at the diaphragm, subcapsular, or perivessel HCC) may be more prone to LTP when RFA is performed. [31–33]. Unfavorable HCC locations result in insufficient ablation margin, leading to a higher risk of LTP after RFA. In our subgroup analyses, when compared with RFA monotherapy, TACE-RFA was associated with lower risks of LTP in selected characteristics of HCCs, including the subphrenic HCCs and perivessel HCCs. However, this study showed that TACE-RFA was not superior to RFA monotherapy for subcapsular HCCs.

In addition, this study also suggested that there was no significant difference in local tumor control in the subgroup analysis of hypervascular HCCs or nonhypervascular HCCs between 2 groups. Although several studies suggested that TACE-RFA could improve overall survival and local tumor control for hypervascular early HCC compared with RFA alone, this study showed that TACE-RFA did not provide better local tumor control than RFA alone for hypervascular HCCs [34,35]. Instead of the factor of ‘hypervascular’, we found that HCCs with well-defined lipiodol deposition by TACE before RFA were associated with a lower LTP rate. This may be explained by the fact that ‘well-defined lipiodol deposition’ rather than ‘hypervascular’ is an essential factor in improving local tumor control. And, ‘well-defined lipiodol deposition’ before RFA depends not only on the factor of ‘hypervascular HCC’, but also on other factors, such as super-selective embolization technique and the time interval between TACE and RFA. Because well-defined lipiodol deposition by TACE could serve as the landmark for creating a sufficient ablation margin for subsequent RFA [36] (Figure 5).

While nonselective TACE with an inappropriate dose of lipiodol and a longer time interval between TACE and RFA could lead to ‘ill-defined lipiodol deposition’, thus reducing the role of ‘intratumor lipiodol deposition’ as a landmark for sufficient ablation margin. In addition, ‘well-defined lipiodol deposition’ could provide a better effect in embolizing the tumor’s blood supply arteries, and contributes to a larger ablation zone by reducing the heat sink effect [37]. It was the synergistic anticancer effect of the combination therapy that enables it to achieve a better local tumor control than RFA monotherapy, especially for larger HCC, subphrenic or perivascular HCC. Therefore, further studies with a larger sample size are warranted to investigate that the benefits of TACE-RFA compared with RFA monotherapy in providing local tumor control for select HCCs, such as HCCs with well-defined lipiodol deposition after TACE or those located in unfavorable locations and the effect of the time interval between TACE and RFA.

Consistent with previous studies, we found that most LTP occurred within the first 3 years following RFA, with the risk of LTP gradually decreasing subsequently [6,26]. In our center, a rigorous follow-up program during the early phase after RFA was in place. Therefore, most cases of LTP were identified early and effective treatments were instituted. However, our results indicated that TACE-RFA did not significantly improve the survival of patients with small HCCs despite lower rates of LTP when compared with RFA monotherapy, in which similar results were also reported by Kim et al. [15].

In this study, there was no difference in the incidence of major complications between the TACE-RFA group and the RFA monotherapy group, although the major complications observed in the TACE-RFA group might also be related to the effects of RFA Adverse incidence associated with TACE for small HCC is rare, which may be attributed to the suprapl.
selective technique of TACE. Nevertheless, coupled with the results from other studies [15,37], our findings have indicated that TACE-RFA is a safe treatment for small HCCs, equivalent to RFA monotherapy.

There were several limitations to our study. Firstly, this was a retrospective and non-randomized study with a small sample size. Therefore, further well-designed studies with a larger sample size are warranted to validate our findings in the subgroup analysis on the potential risk of LTP. Secondly, in this study, the time interval between TACE and RFA was mostly within 4 weeks, but TACE with concurrent RFA was performed in several of our patients. The differences in the time interval between TACE and RFA may lead to biases in the evaluation of treatment efficacy and safety, given that a long interval period may undermine the embolization effect and ‘landmark effect’ of the lipiodol deposition, leading to an underestimation of the effectiveness of TACE-RFA. Thirdly, recurrence-free survival was not evaluated in this study. This was because patients with early-stage HCCs often fall into an ‘on-off-on’ situation – that new HCCs occur during the follow-up period and are typically treated and cured immediately. Fourthly, the assessment for LTP might be biased as a result of different imaging methods, given that CBCT has a lower resolution than CT.

5. Conclusions
TACE-RFA provides a superior local tumor control to RFA monotherapy for selected patients with small HCCs, although this does not lead to better survival outcomes. For HCCs of 2–3 cm in diameter, subphrenic HCCs perivessel HCCs and HCCs with well-defined lipiodol deposition by TACE before RFA, TACE-RFA can be considered as an effective alternative treatment to RFA monotherapy.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Data availability statement
The data that support the findings of this study are openly available in (repository name e.g., ‘figshare’) at http://doi.org/doi, reference number (reference number).

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