Transcatheter chemoembolization plus percutaneous radiofrequency ablation versus laparoscopic radiofrequency ablation: improved outcome for inoperable hepatocellular carcinoma

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ABSTRACT

Aims: To retrospectively compare the efficacy of transcatheter chemoembolization (TACE) plus percutaneous radiofrequency ablation (PRFA) (hereafter, TACE þ PRFA) and laparoscopic radiofrequency ablation (LRFA) in the treatment of inoperable hepatocellular carcinoma (HCC).

Methods: From July 2014 to December 2017, 132 consecutive patients with inoperable HCC were treated with TACE þ PRFA (n = 86) or LRFA (n = 46). Overall survival (OS) and recurrence-free survival (RFS) were analyzed using log-rank test and Cox regression analysis. Propensity score matched (PSM) analyses based on patient and tumor characteristics were also conducted. Additionally, we performed exploratory analyses to determine the effectiveness of TACE þ PRFA and LRFA in clinically relevant subsets.

Results: The baseline characteristics of TACE þ PRFA patients displayed relatively inferior liver status and a higher rate of BCLC-B disease. For unmatched patients, median OS (55.0 vs. 42.0 months; p = .019) and RFS (20.0 vs. 11.0 months; p < .001) were significantly longer in TACE þ PRFA group than that in the LRFA group. After PSM, 39 matched pairs were identified. The difference in median OS (60.0 vs. 44.0 months; p = .009) and RFS (27.0 vs. 11.0 months; p < .001) between the two groups remained significant. Multivariate analysis in matched patients showed that treatment modality and response to initial treatment were significant predictors of OS and RFS, while recurrence after resection was an independent prognostic factor of OS. The benefits of TACE þ PRFA were consistent across all the subgroups examined. The different treatments had a similar complication rate.

Conclusions: Compared to LRFA, TACE þ PRFA results in improved OS and RFS in patients not amenable to resection.

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer fatalities worldwide, claiming the lives of more than 750,000 individuals each year [1]. Among the Asia-Pacific countries, chronic hepatitis B (CHB) with subsequent cirrhosis is the primary cause of HCC [2,3]. Notably, more than 90% of patients with CHB-related HCC are also cirrhotic at the time of diagnosis, presenting with impaired liver function, elevated bilirubin, and portal hypertension [4]. Therefore, the management of HCC involves a delicate decision-making balance to optimize tumor treatment and minimize background liver toxicity.

Radiofrequency ablation (RFA) therapy is the first-line treatment for patients with Barcelona Clinic Liver Cancer (BCLC) very early (0) and early (A) stages or as an alternative strategy for individuals who are not eligible for surgical resection due to poor functional liver reserve [5,6]. RFA can usually be performed percutaneously under imaging guidance. However, laparoscopy is recommended in cases with lesions in high-risk locations for better local control, coupled with a positive but statistically insignificant effect on long-term prognosis [7,8].

Transcatheter chemoembolization (TACE) was introduced as a reference treatment for HCC in the intermediate stage at the beginning, but now can also be an alternative in patients with early-stage HCC unsuitable for ablation or resection [5,9–12]. Moreover, the combination of PRFA and TACE has been used in patients with unresectable HCC in an attempt to enhance the therapeutic effect concomitantly [11,13–15]. The purpose of this investigation was to compare the long-term survival between TACE þ PRFA and laparoscopic radiofrequency ablation (LRFA) alone in the treatment of inoperable early-stage HCC.
Method

Study design and patient selection

This single-center retrospective study was approved by the local hospital ethics committee (UHCT-IEC-SOP-016-02-01). The data were collected anonymously from the electronic medical records, and the requirement for informed consent was therefore waived. From July 2014 to December 2017, 217 consecutive patients with inoperable HCC were treated with either TACE + PRFA (n = 156) or LRFA (n = 61) at Wuhan Union Hospital. The diagnosis of HCC was either biopsy-proven or met the European Association for the Study of the Liver (EASL) imaging criteria [5]. Lesions were deemed inoperable by a multidisciplinary tumor conference. Of the 217 patients, 85 were excluded owing to (a) histology other than HCC, or (b) loss of follow-up after the initial treatment, or (c) incomplete evaluable imaging data at baseline and follow-up. Eventually, the study cohort comprised 132 patients with HCC, 86 who underwent TACE + PRFA and 46 who underwent LRFA (Figure 1).

Treatment protocols

All patients were assessed by multiphasic computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) of the liver within two weeks before treatment and were reviewed by a multidisciplinary tumor conference. All TACE and PRFA procedures were performed by a team of interventional radiologists with no less than ten years of experience, and LRFAs were performed by two surgeons in the hepatobiliary department with at least eight years of laparoscopic experience. TACE was performed before PRFA, and the interval between TACE and PRFA was determined by resolution of the post-embolization syndrome, which usually took 3–5 days.

TACE

TACE was performed under the guidance of digital subtraction angiography (Altis Zee Ceiling, Siemens Medical Solutions, Germany). Plain lidocaine (1%) was injected into the skin and subcutaneous tissues at the femoral artery puncture site and the 5-HT3 antagonist (with or without dexamethasone) was given as antiemetic prophylaxis. After introducing a 5-F catheter (Yashiro, Terumo, Japan; or R-H, Cook, USA) through the common femoral artery, celiac angiography and superior mesenteric arterial portovenography were performed sequentially to identify the arterial blood supply and to confirm patency of the portal vein. A coaxial 2.7-F microcatheter (Progreat, Terumo, Japan) was advanced super selectively in the feeding arteries of tumors to perform chemoembolization by injecting iodized oil emulsion, which usually contained 20–40 mg doxorubicin hydrochloride (Hisun Pharmaceutical Co. Ltd., Zhejiang, China) mixed with 10 ml of lipiodol (Lipiodol Ultrafluido, Guerbet, France). Finally, gelatin sponge particles (300–500 μm, Cook, USA) mixed with contrast medium suspension were used to reach the endpoint of stationary blood flow and Lipiodol saturation of the tumor with visualization of adjacent portal vein radicles.

PRFA

After setting an optimal puncture path with ultrasound or CT, patients were administered local anesthesia (10 ml 1% lidocaine) and analgesia (10 mg of morphine). A RITA 1500 generator (RITA Medical Systems Inc., Mountain View, USA) with a single or multiteried expandable electrode (StarBurst XL, RITA, USA) was employed at our center. For a tumor less than 5.0 cm in diameter, a single or clustered expandable electrode was deployed at the center of the tumor. To secure a 3.0–5.0 cm ablation zone with a safety margin of at least 1 cm around the lesion, an effective ablation time of 15–25 min was required. For tumors larger than 5.0 cm, multiple overlapping ablation zones were required to coagulate the tumor and the surrounding normal parenchyma. Needle tract ablation was performed simultaneously to prevent tumor seeding and hepatic bleeding when withdrawing the electrode.

LRFA

Laparoscopic ablation was performed using the same ablation device as the percutaneous approach. All patients were placed under general anesthesia. Three trocars were placed in the abdomen, through which initial laparoscopic ultrasonography (Flex Focus 800, 4-Way Laparoscopic 8666-RF, BK Medical, Denmark) of the liver was performed to locate the tumor and set the ablation course. Based on the guiding line on the ultrasonogram, the operator introduced the electrode into the tumor and deployed it under ultrasound guidance. Ablation was performed for 5–20 min to ablate all viable tumor tissues and at least 1 cm thick tumor-free margin. For the superficial lesion, the electrode was inserted through the normal liver tissue to prevent tumor pop-up during ablation.

Figure 1. Flowchart showing the patient selection. HCC: hepatocellular carcinoma; PRFA: percutaneous radiofrequency ablation; TACE: transcatheter arterial chemoembolization; LRFA: laparoscopic radiofrequency ablation.
Follow-up protocol

Patients were followed up with liver function test, alpha-fetoprotein (AFP) level (if elevated at first), and imaging with multiphasic CT or MRI as early as 6–8 weeks after initial treatment and every 2–3 months thereafter. Two independent radiologists blinded to each other utilized the modified Response Evaluation Criteria in Solid Tumors (mRECIST) to evaluate treatment response [16], and any conflict in of assessment was resolved by a third radiologist (more senior). When recurrence occurred during the follow-up period, TACE (or/and PRFA if necessary) was repeated every 2–3 months in patients in the TACE+PRFA group to obtain a complete response unless there was evidence of contraindications. Likewise, patients in the LRFA group underwent LRFA or appropriate management as radiotherapy, chemotherapy, or best supportive care depending on their hepatic function and tumor status.

Definitions and evaluation of data

The primary endpoint was overall survival (OS). The secondary endpoints included recurrence-free survival (RFS), radiological response after initial treatment, and complication rate. OS was defined as the interval between the first TACE procedure and either death or the last follow-up (considered censored). RFS was defined as the period between the initial treatment and radiologically confirmed recurrence, either recurring at the ablation site or as the new hepatic lesion. Early recurrence was defined as radiologically confirmed tumor relapse within 12 months of the initial treatment. The first radiological response evaluation was conducted according to mRECIST 6–8 weeks after initial treatment. The objective response (OR) was equivalent to the sum of complete response (CR) and partial response (PR). Stable disease (SD) was considered as the response that did not meet the classification of CR, PR, or progressive disease (PD) according to mRECIST for not less than eight weeks. Following previous research, with respect to multifocal disease, the longest diameter per patient was calculated as the sum of the diameter of the largest and second-largest tumor nodules [17]. The massive lesion in our study was defined as a single mass with the longest diameter greater than 7 cm.

Statistical analysis

All continuous data were described as mean ± standard deviation and were compared using the Student’s t-test. The Mann–Whitney U test was used for nonparametric variables if the assumption of normality was not met. The chi-square test or Fisher’s exact test was used for categorical data.

Propensity score matching (PSM) was performed to minimize the selection bias. A propensity score was calculated for each patient using a logistic regression model with 10 variables concerning the choice of treatment, which included age, albumin, total bilirubin, INR, Child-Pugh class, cause of HCC, BCLC stage, previous treatment, number of lesions, and lesion(s) diameter. To construct a matched cohort, patients treated with TACE+PRFA were matched 1:1 to patients treated by LRFA by using the nearest-neighbor matching algorithm with maximum allowed differences of 2% for propensity scores. Survival curves for OS and RFS were created according to the Kaplan–Meier method and compared using the log-rank test and Gehan-Breslow-Wilcoxon test. A Cox regression model was used to identify the underlying prognostic factors affecting RFS and OS. Risk factors significant at \( p < .10 \) in the univariate analysis were candidates for the multivariate analysis. Among the matched patients, the heterogeneity of treatment effects was assessed with subgroup analysis that explored the effect of age, AFP, BCLC stage, previous treatment, lesion diameter, lesion number, recurrence interval, the response of initial treatment. Statistical analysis was performed using R software version 4.0.5. Statistical significance was set at \( p < .05 \).

Result

Clinical characteristics

The clinical characteristics of the 132 patients and 39 matched pairs (78 patients) after PSM are listed in Table 1. The information of the 161 tumors is summarized in Table 2. The median follow-up duration was 45.0 months in the TACE+PRFA group and 47.0 months in the LRFA group (\( p = .139 \)). Before matching, the TACE+PRFA group included more patients with BCLC-B disease (32.6% vs. 13.0%, \( p = .015 \)), TACE treatment history (27.9% vs. 10.9%, \( p = .024 \)), and Child-Pugh B disease (18.6% vs. 2.2%, \( p = .016 \)) which was consistent with lower albumin (\( p = .035 \)) and higher bilirubin (\( p = .045 \)), and greater lesion(s) diameter per patient (\( p = .005 \)). After matching, no statistically significant differences in any of the preoperative baseline variables were observed between the two groups. It is worth mentioning that virtually all cases with Child-Pugh B class disease were discarded after PSM, and each group contained a BCLC-C disease with a solid pulmonary nodule, which later confirmed metastasis by radiological follow-up. During the follow-up, the median repeated treatment courses of the TACE+PRFA group were three times versus two times for the LRFA group (\( p < .001 \)).

Radiological response and survival outcome

The radiological responses after the initial treatment are listed in Table 3. Although statistically insignificant, the TACE+PRFA group had a higher proportion of ORs in the matched population. The early recurrence rate was significantly higher in the LRFA group than in the TACE+PRFA group in either the matched population (51.3% vs. 23.1%, \( p = .010 \)) or unmatched population (52.2% vs. 31.4%, \( p = .019 \)) (Table 3).

By the end of the observation period, 31 January 2021 half of the subjects in the TACE+PRFA group and 33 subjects (71.7%) in the LRFA group had reached the primary endpoint. The median OS was 55.0 months (95% confidence interval (CI): 43.0–61.0) in the TACE+PRFA group and
The median RFS was 20.0 months (95% CI: 16.0–56.0) in the LRFA group (p < 0.001) (Table 3, Figure 2(a)). The median RFS was 20.0 months (95% CI: 16.0–56.0) in the LRFA group (p < 0.001) (Table 3, Figure 2(a)). Since most censored data appeared in the front of follow-up time, the Gehan-Breslow-Wilcoxon test was also performed to verify the significance of differences (OS: p = 0.030; RFS: p = 0.002 separately). Furthermore, the propensity analysis showed a difference in median OS (60.0 [95% CI: 53.0–Inf] vs. 44.0 [28.0–56.0] months; p = 0.009) and RFS (27.0 [18–37] vs. 11.0 [8–18] months; p < 0.001) between the two groups remained significant and was even more pronounced (Table 3, Figure 3).

### Table 1. Clinical data of unmatched and matched population treated with TACE + PRFA or LRFA.

| Variables                          | Unmatched population | Matched population |
|------------------------------------|----------------------|--------------------|
|                                    | TACE + PRFA (N = 86) | LRFA (N = 46)      | p value | TACE + PRFA (N = 39) | LRFA (N = 39) | p value |
| Gender (M/F)                       | 73 (84.9%)/13 (15.1%)| 40 (87.0%)/6 (13.0%)| .950    | 33 (84.6%)/6 (15.4%)| 34 (87.2%)/5 (12.8%)| 1       |
| Age (range)                        | 55.9 (28–79)         | 54.6 (28–81)       | .813    | 55.9 (32–79)         | 54.6 (28–81)  | .811    |
| Albumin (g/L)                      | 37.8 ± 5.5           | 39.8 ± 4.3         | .035    | 39.4 ± 4.2           | 39.7 ± 4.0    | .932    |
| Total bilirubin (umol/L)           | 19.4 ± 11.0          | 15.8 ± 6.8         | .045    | 16.3 ± 6.7           | 15.9 ± 7.0    | .812    |
| PT (INR)                           | 1.1 ± 0.1            | 1.1 ± 0.1          | .858    | 1.1 ± 0.1            | 1.1 ± 0.1     | .722    |
| AFP (ng/ml)                        | 42.0 months (95% CI: 27.0–56.0) | 39.8 ± 8.4 (84.8%) | .004    | 33 (98.3%)          | .950          |        |
| Previous treatment                 |                      |                    |         |                      |              |        |
| Treatment naïve                    | 48 (55.8%)           | 27 (58.7%)         | .857    | 23 (59.0%)           | 23 (59.0%)    | .998    |
| TACE                                | 24 (27.9%)           | 5 (10.9%)          | .003    | 7 (17.9%)            | 5 (12.8%)     | .993    |
| Lesion number                       |                      |                    |         |                      |              |        |
| Solitary lesion                    | 70 (81.4%)           | 34 (73.9%)         | .033    | 30 (76.9%)           | 29 (74.4%)    | .566    |
| Multifocal disease                 | 16 (18.6%)           | 12 (26.1%)         | .436    | 9 (23.1%)            | 10 (25.6%)    | .881    |
| Location at high-risk area         | 4.6 ± 3.4            | 3.1 ± 1.4          | .005    | 3.3 ± 2.1            | 3.2 ± 1.5     | .998    |
| Median follow-up months            | 45 47               | .139^              | .114    | 43 47               | .115          | .114    |

^aINR: international normalized ratio.
^bIncluding other unknown non-hepatitis B and C causes.
^cLongest diameter per patient was calculated as the sum of diameter of the largest and second-largest tumor nodule if multiple lesion involved.
^dRepeated treatment courses referred to times of TACE procedure (with or without PRFA) and times of LRFA procedure respectively.
^eLog-rank test.

### Table 2. Characteristics of 161 tumors in total.

| Variables                            | TACE + PRFA (N = 100) | LRFA (N = 61) | p value |
|--------------------------------------|-----------------------|---------------|---------|
| Longest diameter (cm)                |                       |               |         |
| Median value                         | 3.2                   | 2.1           | <0.001^ |
| < 3                                  | 46 (46.0%)            | 47 (77.0%)    | <0.001  |
| 3–5                                  | 32 (32.0%)            | 11 (18.0%)    | .052    |
| > 5                                  | 22 (22.0%)            | 3 (4.9%)      | .004    |
| Segmental location^b                 |                       |               |         |
| S1                                   | 0                     | 2 (3.3%)      | .303    |
| S2                                   | 6 (6.4%)              | 2 (3.3%)      | .620    |
| S3                                   | 0                     | 2 (3.3%)      | .303    |
| S4                                   | 5 (5.4%)              | 3 (4.9%)      | .999    |
| S5                                   | 14 (15.1%)            | 12 (19.7%)    | .316    |
| S6                                   | 20 (21.5%)            | 12 (19.7%)    | .784    |
| S7                                   | 21 (22.6%)            | 12 (19.7%)    | .667    |
| S8                                   | 27 (29.0%)            | 16 (26.1%)    | .705    |
| Lobar location (L/R)^c               | 12/85                 | 7/52          | .925    |
| Location at high-risk area           | 34 (34.0%)            | 18 (29.5%)    | .554    |
| Proximity to cholecyst                | 2                     | 6             |         |
| Proximity to vessel                  | 5                     | 4             |         |
| Beneath the diaphragm                | 22                    | 6             |         |
| Inferior tip of the right liver      | 5                     | 2             |         |
| Subcapsular tumor                    | 49 (49.0%)            | 29 (47.5%)    | .857    |

^aMann–Whitney U-test.
^bSeven massive lesions in the TACE + PRFA group are not included for the difficulty of distinguishing segment precisely or multiple segment invasion.
^cThree bi-lobar lesions in the TACE + PRFA group and two of the caudate lobe LRFA group are not listed.

### Univariate and multivariate analyses

The results of OS and RFS in uni- and multivariate analyses for unmatched patients are displayed in Tables 4 and 5, which demonstrate that the longest diameter (hazard ratio [HR], 1.10; 95% CI: 1.01–1.20; p = 0.019), the response of PR (HR, 2.22; 95% CI: 1.26–3.88; p = 0.005), SD (HR, 4.51; 95% CI: 2.11–9.63; p < 0.001), PD (HR, 4.34; 95% CI: 1.75–10.79; p = 0.002), and treatment modality of TACE + PRFA (HR, 0.36; 95% CI: 0.21–0.62; p < 0.001) were significant prognostic factors for OS. Similar to OS, the treatment modality (HR, 0.39; 95% CI: 0.25–0.61; p < 0.001) and longest diameter (HR, 1.15; 95% CI: 1.05–1.27; p = 0.003) were significant for RFS as well in the multivariate analysis. Besides, recurrence after resection (HR, 1.65; 95% CI: 1.04–2.64; p < 0.001) was revealed to be an independent predictor of RFS.
In the propensity score-matched Cox proportional hazard regression analysis (Tables 6 and 7), TACE + PRFA therapy (HR, 0.28; 95% CI: 0.13–0.60; \( p = .001 \)), response of PR (HR, 2.78; 95% CI: 1.26–6.14; \( p = .012 \)), SD (HR, 24.17; 95% CI: 7.58–77.07; \( p < .001 \)), and recurrence after resection (HR, 0.38; 95% CI: 0.17–0.85; \( p = .018 \)) were significant predictors of OS.

With respect to RFS, multivariate analysis revealed that TACE + PRFA therapy (HR, 0.34; 95% CI: 0.16–0.70; \( p = .004 \)), response of PR (HR, 2.57; 95% CI: 1.18–5.63; \( p = .018 \)), and SD (HR, 18.13; 95% CI: 6.13–53.65; \( p < .001 \)) were significant risk factors.

**Subgroup analyses**

In the exploratory subgroup analyses of the matched cohort, the salutary effects of TACE + PRFA on OS were consistent across all subgroups examined. Figure 4 demonstrates the
propensity-matched HRs of TACE + PRFA versus LRFA based on preoperative clinical characteristics and treatment outcomes. However, statistical significance was only observed in the subgroup of patients aged < 55 (p = .004), AFP > 400 ng/ml (p = .014), treatment-naïve (p = .033), diameter greater than 3 cm (p = .014), early recurrence (p = .023) and response to PR (p = .046). In addition, multivariate analysis of the two treatment modalities was conducted separately to determine

| Variables                                      | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
| Male                                           | 0.85 (0.45–1.58)    | .600                  |
| Age > 55 (year)                                | 1.08 (0.68–1.70)    | .748                  |
| Albumin (g/L)                                  | 1.02 (0.98–1.07)    | .391                  |
| Total bilirubin (μmol/L)                       | 0.99 (0.97–1.02)    | .442                  |
| PT (INR)                                       | 0.75 (0.11–5.00)    | .769                  |
| AFP > 400 ng/ml                                | 1.42 (0.76–2.65)    | .276                  |
| Child-Pugh B                                   | 0.79 (0.56–1.30)    | .554                  |
| BCLC stage                                     | 0.99 (0.54–1.81)    | .916                  |
| Cause of hepatocellular carcinoma              |                     |                       |
| Hepatitis B                                    | 0.64 (0.34–1.21)    | .171                  |
| Hepatitis C                                    | 1.14 (0.43–3.04)    | .795                  |
| Nonviral                                       |                     |                       |
| Previous treatment                             |                     |                       |
| Treatment naïve                                | 0.88 (0.50–1.55)    | .660                  |
| Resection                                      | 1.21 (0.69–2.12)    | .516                  |
| TACE                                           | 1.14 (1.07–1.22)    | <.001                 |
| BCLC stage                                     | 1.10 (1.10–1.20)    | .019                  |
| Cause of hepatocellular carcinoma              |                     |                       |
| Hepatitis B                                    | 0.64 (0.34–1.21)    | .171                  |
| Hepatitis C                                    | 1.14 (0.43–3.04)    | .795                  |
| Nonviral                                       |                     |                       |
| Treatment modality (TACE + PRFA)               | 0.58 (0.37–0.92)    | .022                  |

Table 4. Cox regression uni- and multivariate analysis for overall survival of the whole patient.

| Variables                                      | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
| Male                                           | 0.87 (0.50–1.51)    | .615                  |
| Age > 55 (year)                                | 1.00 (0.69–1.46)    | .984                  |
| Albumin (g/L)                                  | 1.01 (0.97–1.05)    | .686                  |
| Total bilirubin (μmol/L)                       | 0.99 (0.97–1.00)    | .126                  |
| PT (INR)                                       | 0.80 (0.19–3.30)    | .756                  |
| AFP > 400 ng/ml                                | 1.46 (0.90–2.38)    | .129                  |
| Child-Pugh B                                   | 0.61 (0.32–1.16)    | .130                  |
| BCLC stage                                     | 1.25 (0.75–2.10)    | .393                  |
| Cause of hepatocellular carcinoma              | 2.15 (1.20–3.84)    | .010                  |
| Hepatitis B                                    | 1.42 (0.19–10.68)   | .733                  |
| Nonviral                                       |                     |                       |
| Previous treatment                             |                     |                       |
| Treatment naïve                                | 1.63 (1.04–2.57)    | .034                  |
| Resection                                      | 1.07 (0.66–1.73)    | .779                  |
| TACE                                           | 1.11 (1.05–1.18)    | <.001                 |
| Multifocal disease                             | 1.57 (1.01–2.44)    | .045                  |
| Response of initial treatment                  |                     |                       |
| CR                                             | 1.91 (1.11–3.29)    | .019                  |
| PR                                             | 5.95 (3.09–11.44)   | <.001                 |
| SD                                             | 3.11 (1.34–7.22)    | .008                  |
| PD                                             | 0.58 (0.37–0.92)    | .022                  |

Table 5. Cox regression uni- and multivariate analysis for recurrence-free survival of whole patient.

propensity-matched HRs of TACE + PRFA versus LRFA based on preoperative clinical characteristics and treatment outcomes. However, statistical significance was only observed in the subgroup of patients aged < 55 (p = .004), AFP ≤ 400 ng/ml (p = .014), treatment-naïve (p = .033), diameter greater than 3 cm (p = .014), early recurrence (p = .023) and response to PR (p = .046). In addition, multivariate analysis of the two treatment modalities was conducted separately to determine

| Variables                                      | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
| Male                                           | 0.87 (0.50–1.51)    | .615                  |
| Age > 55 (year)                                | 1.00 (0.69–1.46)    | .984                  |
| Albumin (g/L)                                  | 1.01 (0.97–1.05)    | .686                  |
| Total bilirubin (μmol/L)                       | 0.99 (0.97–1.00)    | .126                  |
| PT (INR)                                       | 0.80 (0.19–3.30)    | .756                  |
| AFP > 400 ng/ml                                | 1.46 (0.90–2.38)    | .129                  |
| Child-Pugh B                                   | 0.61 (0.32–1.16)    | .130                  |
| BCLC stage                                     | 1.25 (0.75–2.10)    | .393                  |
| Cause of hepatocellular carcinoma              | 2.15 (1.20–3.84)    | .010                  |
| Hepatitis B                                    | 1.42 (0.19–10.68)   | .733                  |
| Nonviral                                       |                     |                       |
| Previous treatment                             |                     |                       |
| Treatment naïve                                | 1.63 (1.04–2.57)    | .034                  |
| Resection                                      | 1.07 (0.66–1.73)    | .779                  |
| TACE                                           | 1.11 (1.05–1.18)    | <.001                 |
| Multifocal disease                             | 1.57 (1.01–2.44)    | .045                  |
| Response of initial treatment                  |                     |                       |
| CR                                             | 1.91 (1.11–3.29)    | .019                  |
| PR                                             | 5.95 (3.09–11.44)   | <.001                 |
| SD                                             | 3.11 (1.34–7.22)    | .008                  |
| PD                                             | 0.58 (0.37–0.92)    | .022                  |
prognostic factors for the specific procedure. Apart from the fact that the initial response remained significant, the repeated treatment courses and early recurrence were the common prognostic factors for both modalities (Table 8).

Complication
All complications in the two groups are listed in Table 9. No treatment-related mortality was documented in any of the

**Table 6.** Cox regression uni- and multivariate analysis for overall survival of matched population.

| Variables                      | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|----------------------|
|                                | HR (95% CI)         | p value              |
| Male                           | 1.13 (0.47–2.72)    | .779                 |
| Age > 55 (year)                | 1 (0.98–1.03)       | .884                 |
| Albumin (g/L)                  | 0.97 (0.89–1.05)    | .398                 |
| Total bilirubin (µmol/L)       | 1 (0.96–1.06)       | .855                 |
| PT (INR)                       | 4.24 (0.12–146.1)   | .424                 |
| AFP > 400 ng/ml                | 1.42 (0.63–3.22)    | .400                 |
| BCLC stage                     | Ref                 | Ref                  |
| A                              | 1.09 (0.51–2.35)    | .817                 |
| B                              | 2.68 (0.93–7.71)    | .068                 |
| C                              | 2.82 (0.34–23.19)   | .334                 |
| Cause of hepatocellular carcinoma |                  |                      |
| Hepatitis B                    | 0.50 (0.23–1.06)    | .070                 |
| Hepatitis C                    | 0.93 (0.40–2.19)    | .872                 |
| Previous treatment             | Ref                 | Ref                  |
| Treatment naïve                | Ref                 | Ref                  |
| Resection                      | 0.69 (0.31–1.53)    | .367                 |
| TACE                           | 1.20 (0.32–4.53)    | .792                 |
| Lesion(s) diameter per patient (cm) |      | .044                 |
| Multifocal disease             | 1.38 (0.67–2.86)    | .384                 |
| Early recurrence               | 1.47 (0.78–2.78)    | .234                 |
| Response of initial treatment  | Ref                 | Ref                  |
| CR                             | Ref                 | Ref                  |
| CR                             | Ref                 | Ref                  |
| PR                             | 1.60 (0.79–3.24)    | .193                 |
| SD                             | 14.07 (5.42–36.57)  | <.001                |
| PD                             | 0.67 (0.09–5.22)    | .702                 |
| Treatment modality (TACE + PRFA) | 0.44 (0.23–0.84)    | .013                 |

**Table 7.** Cox regression uni- and multivariate analysis for recurrence-free survival of matched population.

| Variables                      | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|----------------------|
|                                | HR (95% CI)         | p value              |
| Male                           | 1.2 (0.57–2.53)     | .636                 |
| Age > 55 (year)                | 1 (0.98–1.02)       | .926                 |
| Albumin (g/L)                  | 1.01 (0.95–1.06)    | .849                 |
| Total bilirubin (µmol/L)       | 0.99 (0.96–1.03)    | .702                 |
| PT (INR)                       | 1.11 (0.09–13.08)   | .933                 |
| AFP > 400 ng/ml                | 1.38 (0.72–2.66)    | .337                 |
| BCLC stage                     | Ref                 | Ref                  |
| A                              | 1.33 (0.72–2.44)    | .362                 |
| B                              | 2.80 (1.23–6.38)    | .141                 |
| C                              | 1.48 (0.19–11.42)   | .705                 |
| Cause of hepatocellular carcinoma |                  |                      |
| Hepatitis B                    | 1.01 (0.49–2.07)    | .978                 |
| Hepatitis C                    | 1.47 (0.44–4.84)    | .530                 |
| Previous treatment             | Ref                 | Ref                  |
| Treatment naïve                | Ref                 | Ref                  |
| Resection                      | 1.39 (0.80–2.40)    | .239                 |
| TACE                           | 0.99 (0.49–2.01)    | .983                 |
| Lesion(s) diameter per patient (cm) |      | 1.25 (1.09–1.42)    | <.001                |
| Multifocal disease             | 1.25 (0.72–2.17)    | .427                 |
| Response of initial treatment  | Ref                 | Ref                  |
| CR                             | Ref                 | Ref                  |
| CR                             | Ref                 | Ref                  |
| PR                             | 1.74 (0.99–3.03)    | .053                 |
| SD                             | 11.66 (5.46–24.94)  | <.001                |
| PD                             | 27.65 (3.33–229.67) | .002                 |
| High risk lesion involvement   | 0.67 (0.41–1.10)    | .109                 |
| Subcapsular tumor              | 1.08 (0.66–1.75)    | .763                 |
| Treatment modality (TACE + PRFA) | 0.44 (0.27–0.72)    | .001                 |
Discussion

Since its introduction as a curative treatment for HCC, ablation therapy has shown outstanding performance comparable to resection but is less invasive and more cost-effective in early-stage HCC [18,19]. To our knowledge, this is the first time that the long-term survival data have been compared between TACE + PRFA and LRFA in the treatment of inoperable HCC. The results of this study, although retrospective, support that TACE + PRFA may be a preferable treatment option for early-stage HCC not amenable to resection. This is strengthened by the fact that patients treated with TACE + PRFA had larger tumors and more limited liver function at baseline, with no increase in toxicity from the combined treatment approach.

Cox regression analysis showed that tumor diameter was inversely related to OS and RFS. This observation of a significant influence of tumor size on local recurrence and survival has been reported by others with regard to more extensive series [20,21]. Evidence suggests that with the electrode fully deployed (5 cm), the necrotic area was one-third smaller than anticipated, eventually leading to local recurrence eventually [22]. However, it is no longer a significant risk factor for PSM. This may be partially due to the fact that the diameter range of the tumor was narrowed down and relatively large lesions were discarded. Furthermore, the exacerbation of the initial response in this study was consistent with the worsening outcome. Compared to patients with the first response of CR, the risk of death increased 2.22, 4.51, and 4.34 times of patients with PR, SD, and PD, respectively, and the HR was further increased in the propensity score-matched analysis. Of note, the response of PD became insignificant because only one patient with progressive disease entered the matched cohort.

It is worth mentioning that, before matching, though being linked to inferior initial response, the TACE + PRFA group still surpassed the LRFA group in OS and RFS, which seems inconsistent with the regression model. First, we believe that the unfavorable response of the combination group was attributed to a significantly higher proportion of lesions > 5 cm. Following the consensus from the Society of Interventional Radiology, two or three TACE sessions are scheduled for localized tumors > 6 cm to avoid systemic embolization and acute tumor lysis syndrome [23]. The propensity analysis that excluded patients with relatively larger lesions revealed that the proportion of OR in TACE + PRFA was actually higher than that of LRFA (p = 0.209). Thus, the timing for the first evaluation may require a postponement in such a population carrying large lesion(s) scheduling for the repeated treatment courses proved the protective factors against OS, the improved outcome may be ascribed to the fact that most individuals in the TACE + PRFA group underwent more treatment sessions than the LRFA group (median 3 vs. 2). The LRFA procedure is challenging to repeat as frequently as TACE because of intolerance of patients with impaired liver function to general anesthesia and unaffordable costs. In addition to these factors, the reluctance of surgeons to operate on patients with severe peritoneal

patients. The LRFA group experienced a relatively higher incidence rate of complications than the TACE + PRFA group, although this difference was not significant (8.1% vs. 15.2%, respectively, p = .336). Interestingly, the only patient with hypoalbuminemia was also concomitant with genital swelling concurrently and returned to normal after IV albumin.

Figure 4. Forest plot depicting hazard ratios of TACE + PRFA versus LRFA for inoperable hepatocellular carcinoma in the matched study population.

Table 8. Multivariate analysis by treatment modality for overall survival.

| Variables                  | TACE + PRFA (HR 95% CI) | p value | LRFA (HR 95% CI) | p value |
|---------------------------|-------------------------|---------|-----------------|---------|
| Child-Pugh B              | NS                      |         | NS              |         |
| BCLC stage                | NS                      |         | NS              |         |
| A                         | NS                      |         | NS              |         |
| B                         | NS                      |         | NS              |         |
| C                         | NS                      |         | NS              |         |
| Previous treatment        |                         |         |                 |         |
| Treatment naive           |                         |         |                 |         |
| TACE                       | 1.11 (1.01–1.23)         | .047    |                 |         |
| Longest diameter (cm)     | 3.16 (1.34–7.46)         | .025    |                 |         |
| Multifocal disease        |                         |         |                 |         |
| Early recurrence          | 3.66 (1.18–11.38)        |         |                 | .025    |
| Response of initial treatment |                   |         |                 |         |
| CR                        | Ref                     |         | Ref             |         |
| PR                        | 3.21 (1.35–7.6)          | .008    | 2.83 (0.94–8.49) | .064    |
| SD                        | 5.32 (1.28–22.02)        | .021    | 6.28 (1.86–21.23) | .003    |
| PD                        | 2.17 (0.67–7.08)         | .199    | NA              | NA      |
| Repeated treatment courses| 0.81 (0.71–0.93)         | .002    | 0.25 (0.13–0.47) | <.001   |

Table 9. The comparison of complication between two treatment groups.

|                      | TACE + PRFA (N = 86) | LRFA (N = 46) | p value |
|----------------------|----------------------|---------------|---------|
| Acute liver failure  | 1 (1.2%)             | 2 (4.3%)      | .577    |
| Sepsis               | 2 (2.3%)             | 5 (10.9%)     | .093    |
| Hemorrhage           | 1 (1.2%)             | 0             | 1       |
| Hypoalbuminemia      | 1 (1.2%)             | 0             | 1       |
| Biloma               | 1 (1.2%)             | 0             | 1       |
| Total                | 7 (8.1%)             | 7 (15.2%)     | .336    |
adhesions was another restraint to the repetition of LRFA procedure. Even so, among the 46 patients in the LRFA group, 35 (76%) underwent LRFA procedure twice.

Several studies have concluded that TACE + PRFA is a promising alternative for patients with massive lesions without additional safety issues [24,25]. Although statistically insignificant in this study, the TACE + PRFA group appeared to have better survival outcomes than the LRFA group with regard to high-risk lesion involvement (Figure 5). The enhanced efficacy may be attributed to the weakening of the heatsink effect, which refers to the cooling effect of blood flow around the ablation zone. Furthermore, lipiodol used in TACE reduces the portal flow around the tumor by filling the peripheral portal vein via the peribiliary plexus (a type of arterioportal communication) [26]. Consequently, the coagulated area induced by radiofrequency ablation may increase. Of note, the lesion at the lower edge of segment VI, or the tip of the liver as we refer to, is considered high-risk in this investigation, which is rarely reported by anyone else. Since proximity to the hepatic flexure usually correlates with the escalating risk of intestinal perforation, ablation in this area is performed selectively.

The limitations of the present study are mainly associated with the insufficiency and inequality of sample size between the two treatment groups, even with PSM, to reduce the selection bias. Therefore, a larger-scale prospective controlled trial with a rigorous design and more indicative clinical features is warranted to validate our findings.

In conclusion, TACE combined with PRFA may provide improved outcomes for patients with inoperable HCC, hence giving priority to this therapeutic combination over LRFA.

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Figure 5. Kaplan–Meier curves show overall survival (a) and recurrence-free survival (b) in patients with high-risk area lesions in the TACE + PRFA and LRFA groups.
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